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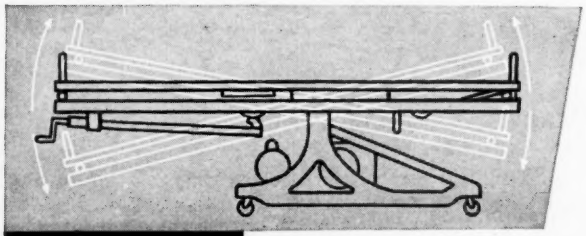

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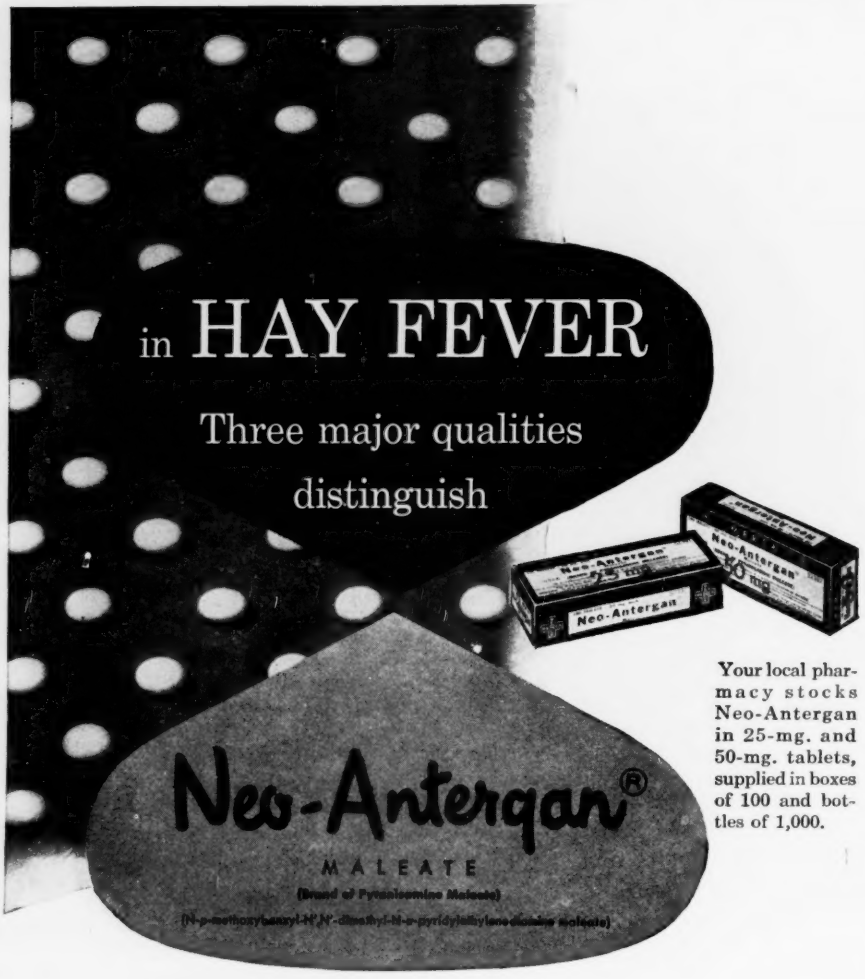

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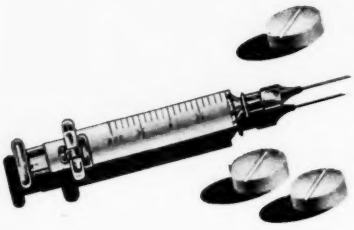

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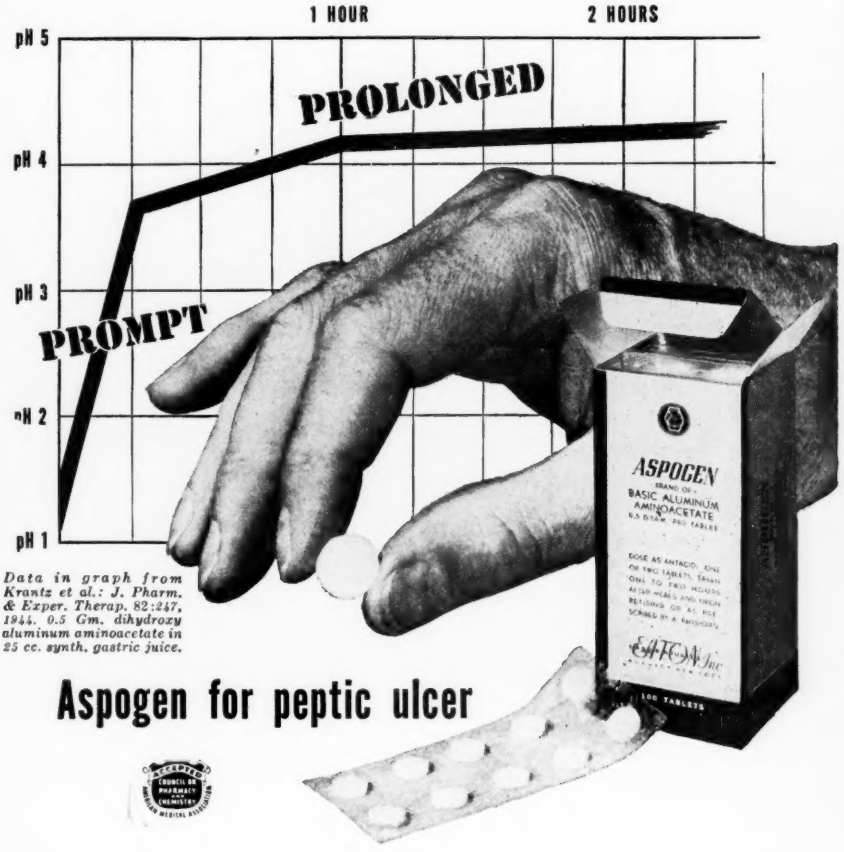
*Holbert, J. M., Noble, N. and Grote, I. W.: *A Study of Antacid Buffers. II. Prolonged Neutralization*, J. Am. Pharm. A. (Sci. Ed.) *37*:292, 1948.



Data in graph from Krantz et al.: J. Pharm. & Exper. Therap. 82:247, 1944. 0.5 Gm. dihydroxy aluminum aminoacetate in 25 cc. synth. gastric juice.

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RESEARCH IN THE SERVICE OF MEDICINE

ARCHIVES of INTERNAL MEDICINE

VOLUME 83 MAY 1949 NUMBER 5

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IRON OVERLOAD (HEMOSIDEROSIS) AGGRAVATED BY BLOOD TRANSFUSIONS

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F. JONES, M.T.

AND

J. M. HILL, M.D.

DALLAS, TEXAS

TWO TYPES of excessive iron deposits in the body are usually distinguished. The widespread iron deposition associated with prolonged hemolysis or following the repeated experimental injection of hemoglobin solution intravenously has been designated as hemosiderosis. The term hemochromatosis has been reserved for a special entity in which the most common features have been widespread iron deposition (hemosiderin pigment); hemofuscin deposits; increased copper content of tissues; cirrhosis and hypogonadism; pancreatic damages ("pancreatic cirrhosis") and diabetes mellitus, and skin pigmentation. These features of hemochromatosis have varied in their intensity and also in the frequency of their combination.

With the advent of blood banks and the greater confidence in blood transfusion therapy, larger volumes of blood are being administered. Under special conditions it is possible for prolonged transfusion therapy to be associated with a prominent iron overload of various tissues. In certain organs this metallic excess is associated with parenchymatous damage.

The present discussion treats especially of the iron overload of anemic patients requiring transfusions over prolonged intervals. Five closely studied cases in which autopsies were subsequently performed are reported.

REPORT OF CASES

CASE 1.—A 37 year old white woman was observed over a twelve and a half month period. The main original complaints were weakness for three months and jaundice for six weeks. She had noted aching in the arms and legs and fever but no chills. Prior to her admission to the hospital, liver and iron therapy and 3,200 cc. of blood had failed to alter the course.

The patient was well nourished and displayed prominent jaundice of the skin and scleras. The pulmonary fields were clear, and a grade III apical systolic mur-

From the William Buchanan Blood Center.

TABLE 1.—*Initial and Follow-Up Hematologic Data on Case 1* *

Day	Blood, Cc.	Red Blood Cell Count	Hemoglobin, Gm./100 Cc.	Hematocrit, Percentage	Mean Corpuscular Volume, Cu. μ Mean Corpuscular Hemoglobin, γγ Mean Corpuscular Hemoglobin Concentration, Cc./100 Cc.	Reticulocytes, Percentage	Icterus Index	Stool Urobilinogen,† Mg./100 Cc.	White Blood Cell Count per Cu. Mm.	Polymorphonuclear Cells, Percentage	Platelets per Cu. Mm.	Temperature Pulse Respirations
1	1,000	1,990,000	5.6	21	105.5 28 26.6	20	..	.....	.....	..	.....	100 90 20
3	.....	.....	12.95	..	.....	..	..	.....	17,050	85	.....	100.4 94 22
9-10	1,000	2,230,000	6.9	..	.....	14.8	20	2,048	23,350	82	391,000	102 95 25
11-14	2,000	3,770,000	11.4	..	.....	..	..	673	18,600	82	368,000	101.4 95 25
28	.....	2,660,000	8.55	..	.....	..	..	305	14,400	64	.....	98.6 76 18
90-91	.....	1,870,000	6.25	..	.....	30	20	1,400	25,000	72	.....	99.2 85 20
114	.....	2,020,000	5.3	..	108.9 26 25	28	..	1,350	36,300	48	.....	99 85 18
117	1,500	2,080,000	7.2	..	.....	..	..	.....	.....	..	.....	..
120-121	.....	4,140,000	11.75	..	.....	..	18	2,520	8,300	37	.....	98.6 70 15
272	1,500	.....	6.6	..	.....	14	14	.....	13,000	65	.....	100.2 100 25
309	.....	1,960,000	6.6	..	.....	18	..	.....	20,800	38	.....	99.6 95 20
310-325	4,500	.....	7.3	..	.....	..	..	.....	.....	..	.....	100.2 85 20
329	.....	2,260,000	7.55	..	.....	10	..	1,026	.....	..	.....	98.6 80 18
333-348	8,500	2,530,000	8.85	25	99 34 35	..	..	.....	.....	..	.....	98.8 75 18
360-378	9,000	1,950,000	6.25	..	.....	..	427	.....	.....	..	.....	101.2 100 20
379	.....	.....	7.9	..	.....	..	571	.....	.....	..	.....	101 100 20

* These data represent periodic cross sectional samples taken from a number of determinations. The data were similar at all times.

† This was determined by the Sparkman technic.

mur was heard. The spleen was palpated 2.5 cm. below the costal margin. The main hematologic data can be noted in table 1. In addition the bone marrow (sternum) showed marked erythroid hyperplasia. A diagnosis of acute hemolytic anemia was made, and splenectomy (Dr. J. V. Goode) was performed. The spleen demonstrated a prominent degree of congestion, dispersed follicles and no outstanding disturbance of reticuloendothelial elements. On the third postoperative day the hemoglobin concentration was 12.95 Gm. per hundred cubic centimeters, higher than throughout the remainder of the patient's course. Pain in the chest, an oral temperature of 102 F. and other symptoms at this time were compatible with pulmonary infarction. These symptoms receded, and on the twenty-eighth day the patient was discharged afebrile but still anemic. The phenolsulfonphthalein test and urea-clearance tests elicited normal reactions, the cholesterol-cephalin flocculation test gave a 2 plus reaction and the hippuric acid test showed 30 per cent excretion. Four thousand cubic centimeters of blood had been given on this admission.

Three months after splenectomy the patient complained of shortness of breath, swelling of the feet and ankles, weakness and jaundice. Evidence of severe hemolytic anemia persisted (table 1). A differential count on the sternal marrow yielded the following percentage figures: megaloblasts, 1.5; erythroblasts, 14; normoblasts, 50 (total erythroid, 65.5); myeloblasts, 1; myelocytes, 4; neutrophils, 24; eosinophils, 3.5; plasma cells, 0.5, and megakaryocytes, 1.5 (total white cells, 34.5). Nucleated red cells in the peripheral blood fluctuated between 4 and 14 per hundred white cells. One month later transfusions were again given (1,500 cc.), with only temporary benefit. An exploratory laparotomy failed to demonstrate an accessory spleen.

The hemolysis continued unabated, and as a final resort the anemia was treated with repeated blood transfusions. During the final two and a half months a total of 22,000 cc. of blood was given. Relief of the anemia was evanescent, and the red blood cell count varied between 1,200,000 and 2,500,000 and the hemoglobin concentration between 4 and 7.9 Gm. per hundred cubic centimeters (fig. 1).

Toward the end it became difficult to obtain completely compatible blood for this patient. Transfusion reactions became frequent even with seemingly compatible blood. On one occasion 100 pints (47 liters) were tested before 1 compatible pint was discovered. During the final stay in the hospital, two complications were overcome, phlebothrombosis of the left lower extremity and benign tertian malaria. The malaria yielded rapidly to therapy with quinacrine hydrochloride and quinine. (The malaria likely resulted from the transfusion therapy, although the patient originated from an area of Texas where malaria is endemic.)

Additional medication during the final three months included crude liver extract intramuscularly (15 units weekly); folic acid (15 mg. daily); ferrous gluconate (1 Gm. daily for twenty-five days); methionine and choline (3 Gm. daily); vitamins B and C, and penicillin. A low grade fever and evidence of hemolysis persisted. Frequent tests of the urine failed to demonstrate hemoglobin. The reaction to the acid hemolysis test was negative. Daily urinalysis revealed a lowered and fixed specific gravity, 1.005 to 1.013, moderate proteinuria and periodic acetonuria. Moderate azotemia was constant terminally (nonprotein nitrogen, 60 mg. per hundred cubic centimeters). The icterus index continued to rise and reached a peak of 571. The color of the skin became a mixture of brown and yellow. Twitching and jerking of thigh and leg muscles developed, and the patient became comatose and died quietly.

Findings at Autopsy.—The autopsy was performed one hour after death.

Gross Examination: There was intense jaundice everywhere. The abdominal surgical wounds were well healed. The heart (weight, 310 Gm.) was not remark-

able. The right lung (weight, 210 Gm.) was crepitant and air containing throughout. The left lung (weight, 210 Gm.) showed 50 per cent atelectasis of both lobes and a recent hemorrhage of the lower lobe measuring 3 by 1.5 by 1.5 cm. The liver (weight, 2,400 Gm.) extended 4 cm. below the costal margin in the midclavicular line and was dark green. On section the lobular markings were distinct, being characterized by greenish brown centers 1 to 2.5 mm. wide surrounded by a gray mantle 0.5 to 1 mm. wide. The liver substance was moderately friable. The gallbladder was distended with black bile which contained myriads of fine pigment stones resembling coffee grounds. The bile passages were patent. The spleen was absent; there were no accessory spleens. The gastrointestinal tract and pancreas were of normal appearance. The kidneys (weight of right one, 250 Gm.; weight of left one, 270 Gm.) were similar. The cut surface bulged, the capsule stripped

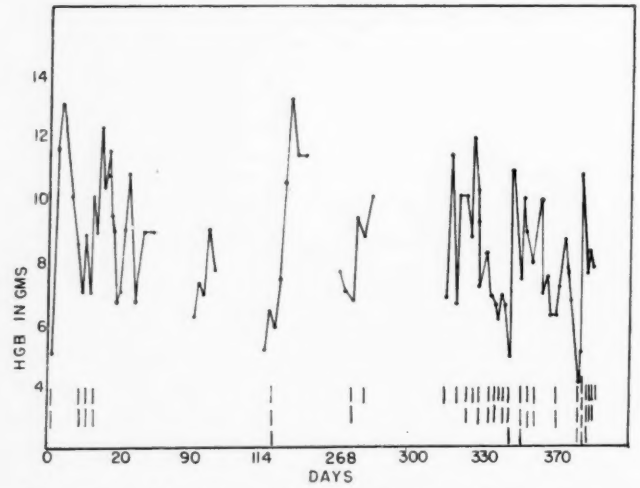

Fig. 1.—The peripheral hemoglobin concentration throughout the course in case 1. Each line below represents 500 cc. of blood given as a transfusion. Note the frequent lowering of the hemoglobin concentration demonstrating the continuous hemolytic activity. Anemia was severe throughout.

readily leaving a smooth surface, the cortex was dark green and stood out vividly and the medulla was grayish. The adrenals showed opaque, gray, friable cortex. All visceral lymph nodes were enlarged and soft and had prominent brown medullae. The femoral bone marrow was extremely hyperplastic. A subarachnoid hemorrhage over the left cerebral hemisphere extended from the anterior pole posteriorly for 4 cm. and deep into the brain tissue. The lungs, liver, lymph nodes, and kidneys gave a 4 plus reaction to Perles' test for iron. A heart blood culture was sterile after twenty-one days.

Microscopic Examination: The myocardial fibers showed mainly an increase in the pigment at the nuclear poles. All lung sections demonstrated interstitial fibrosis, round cell infiltration and a decrease in vascularity (chronic pneumonitis). The alveolar walls were thick in some areas. Emphysema was also prominent in

other areas. A reticulum stain demonstrated an increase in alveolar wall reticulum. A moderate amount of interstitial hemosiderin deposit existed. One lobe displayed a recent pulmonary hemorrhage. The liver was markedly damaged. There was destruction and collapse of the centers of the lobules. Numerous hemosiderin-laden

Fig. 2.—*A*, section of lung from case 1. The following are depicted: interstitial fibrosis, decreased vascularity, hemosiderin deposits, the infiltration by round cells (pneumonitis) and emphysema. *B*, reticulum stain of section of lung from case 1. Note the heavy reticulum pattern of the alveolar walls (fibrosis). × 50.

cells were present here, the hemosiderin being deposited in both Kupffer and parenchymal cells. An iron stain emphasized the greater amount of iron pigment to be in or near the collapsed lobular centers. Larger, hyperchromatic parenchymal cells suggested early regeneration. In the portal areas there was evidence of proliferation of bile ducts, slight fibrosis and a moderate collection of round cells. From the apparent degree of microscopic hepatic destruction, approximately 30 per cent of the parenchyma seemed to be remaining. Hemosiderin was seen within bile duct epithelium. There was slight fatty metamorphosis of the intact cells. The kidneys demonstrated an outstanding amount of hemosiderin within the epithelial cells of the proximal segment, but some pigment was also found in distal segments. The glomeruli were intact. The lumens of the proximal segments contained a granular debris and that of the distal segments frequently accommodated pigmented (brownish green) casts. The interstitial tissue was not accentuated. The blood

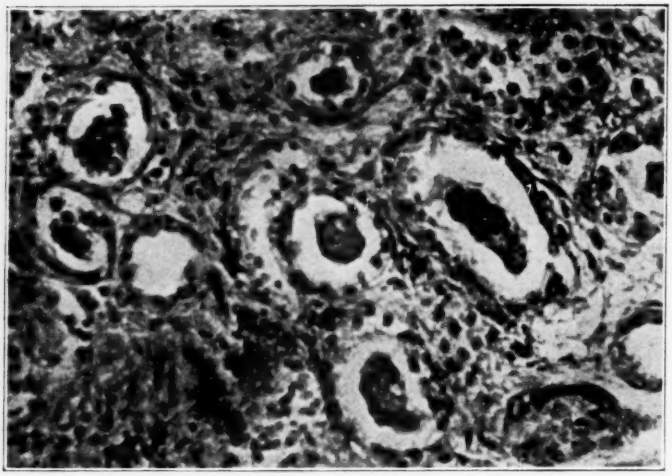

Fig. 3.—Section of kidney from case 1 showing iron-containing casts and degeneration of tubules.

vessels were normal. One pelvis revealed recent hemorrhage and slight pyelitis. There was chronic cystitis. The pancreas had a definite but not pronounced accumulation of hemosiderin pigment within acinar cells. The islet tissue appeared undisturbed. The adrenal glands were the seat of slight cortical atrophy and marked pigmentation of the deeper cortical layers (reticularis and inner fasciculata). The pituitary and the ovary were normal. A lymph node demonstrated prominent reticuloendothelial hyperplasia, with the filling in of the sinuses by macrophage-like cells heavily laden with hemosiderin pigment. The brain showed a recent hemorrhage.

Case 2.—A white man, aged 38 years, complained of weakness of two years' duration and of jaundice and epigastric pain of eight months' duration. He was observed to be anemic and was given liver therapy and "frequent blood transfusions," the specific amounts not being known. Loss of weight amounted to 33

pounds (15 Kg.). The patient was markedly icteric. The spleen and liver were palpable. Aside from evidence of loss of weight, there were no remarkable findings. The hematologic data are given in table 2. The Kline, Kahn and Wassermann tests gave a 4 plus reaction (likely false positive). The diagnosis of hemolytic anemia was made, and a splenectomy was performed on the ninth day. The spleen weighed 550 Gm., and an accessory spleen weighed 50 Gm. Follicular hyperplasia and large

TABLE 2.—*Initial and Follow-Up Hematologic Data on Case 2*

Day	Blood, Cc.	Red Blood Cell Count	Hemoglobin, Gm./100 Cc.	Hematocrit, Percentage	Mean Corpuscular Volume, Cu. μ Mean Corpuscular Hemoglobin, $\gamma\gamma$ Mean Corpuscular Hemoglobin Concentration, Cc./100 Cc.	Reticulocytes, Percentage	Icterus Index	Stool Urobilinogen, Mg./100 Cc.	White Blood Cell Count per Cu. Mm.	Polymorphonuclear Cells, Percentage	Platelets per Cu. Mm.	Temperature Pulse Respirations	Bile Urine
1	.....	2.04	6.25	20	98 30.6 30.2	34.5	...	.....	7,800	40	141,800	99.4 96 18	...
5	1,000	2.5	5.95	..	....	....	...	2,268	.....	..	.....	96.6 90 22	...
6-8	1,000	2.9	8.25	23	79 28.3 35.8	5.4	...	.....	.....	..	307,400	101 100 18	...
15	3,000	2.07	6.9	25	120.1 33.3 27.6	11	50	1,980	.....	..	289,450	98.6 80 18	...
22	3,500	4.15	12.65	..	....	....	276	.....	.....	..	.....	98.6 80 18	4+
23-26	2,000	4.1	12	..	88.3 29 32.7	10	432	.....	.....	..	371,000	98.6 80 20	4+
30	1,500	1.98	6.25	..	....	....	368	2,142	26,200	71	.....	99.2 88 18	4+
36	2,500	2.19	6.9	28	127 31.5 24.6	....	368	1,326	.....	..	273,750	99 90 18	4+
43	4,050	3.7	11.4	34	91.8 30.8 34.8	....	384	970	.....	..	475,800	100.2 80 20	...
44-48	2,000	3.09	10.15	..	....	....	430	1,890	.....	..	395,200	98.6 90 20	4+
51-57	6,500	3.64	11.1	..	113 37 30.5	....	460	1,575	.....	..	308,000	100.6 90 18	4+

"germinal" centers, decided congestion and prominent accumulations of hemosiderin pigment were present in the spleen. The reticuloendothelial elements were only slightly increased in the pulp.

Evidence of hemolysis persisted after splenectomy, and the anemia remained severe. Blood transfusions were resorted to. During the subsequent two month period, 26,000 cc. of blood were given, and 61 units (each 17.5 Gm.) of plasma were also given for nutrition. In addition the patient received crude liver extract, vitamins and penicillin.

The anemia persisted (fig. 4), and the patient became intensely jaundiced (icterus index, 460). The skin became bronze in color. The urinary output was adequate, but terminally there was moderate evidence of renal insufficiency (urea clearance, 70 per cent; blood urea, 58 mg. per hundred cubic centimeters; urine specific gravity, 1.012, and proteinuria, 30 mg. per hundred cubic centimeters). On the fifty-first day the patient became restless, later lethargic and then irrational, and terminally he had convulsions. He died on the sixty-first day in the hospital.

Findings at Autopsy.—Gross Examination: There was intense jaundice everywhere. The surgical incision was well healed. The heart was flabby but otherwise not remarkable. The lungs were free and crepitant and displayed no hyperemia or edema. The liver (weight, 2,170 Gm.) was dark green. The lobular markings were distinct. The gallbladder was free of stones. The gastrointestinal

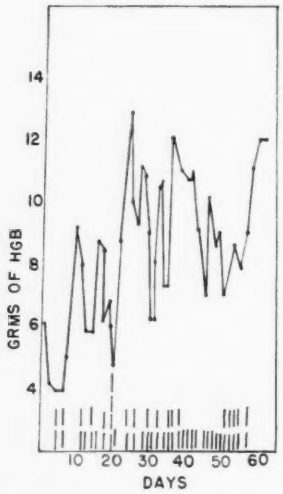

Fig. 4.—The peripheral hemoglobin concentration throughout the course in case 2. As in case 1, there is a frequent fluctuation indicating continuous hemolysis. The transfusion therapy was only transiently effective, and the anemia was severe throughout.

tract and pancreas were grossly unaltered. The kidneys (right one, 390 Gm.; left one, 290 Gm.) were similar. The cut surface bulged, the capsule stripped with ease leaving a smooth surface and the cortex was dark green. The visceral lymph nodes were enlarged, soft and reddish brown. The sternal, vertebral and femoral bone marrow was markedly hyperplastic. The brain was unaltered save for a moist appearance.

Microscopic Examination: The myocardium displayed interstitial edema and a focal collection of round cells and macrophages (focal myocarditis). The lungs demonstrated a moderate interstitial fibrosis (increase in reticulum) and infiltration with small round cells and many pigment-laden macrophages. An iron stain showed iron deposit in the connective tissue. The liver was prominently disorganized. There was a heavy accumulation of hemosiderin within the parenchymal cells

and in Kupffer cells. The central portions of the lobules were disorganized and collapsed. Here the condensed connective tissue had the bluish appearance of precipitated free iron. An iron stain showed a heavy deposit of iron throughout the lobule, mostly within cells. A reticulum stain showed a generalized increase in reticulum fibers. The portal areas displayed a moderate increase in connective tissue, round cell infiltration and evidence of bile duct proliferation. Hemosiderin was seen within the epithelium of an occasional bile duct. In the kidneys an intense accumulation of hemosiderin was present within the tubular epithelium of all levels but more marked in the proximal segment. There were many greenish

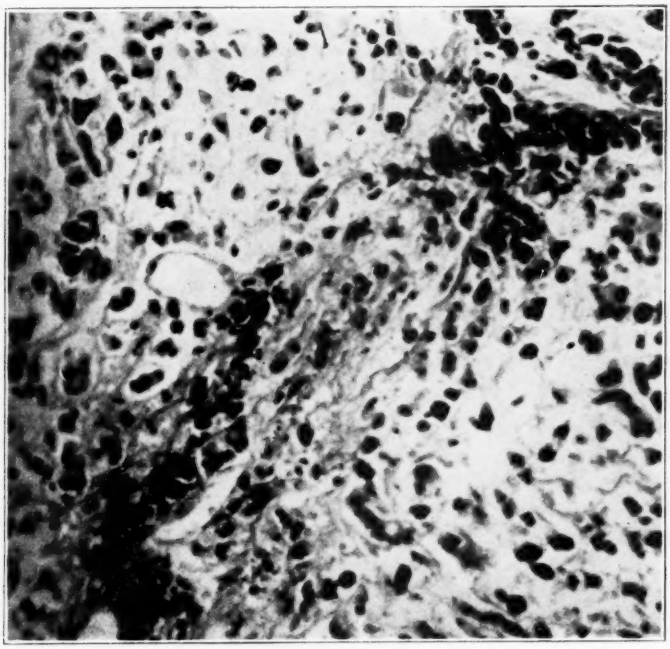

Fig. 5 (× 50; iron stain).—Section of liver from case 2 showing destroyed and collapsed central portion of hepatic lobules and the heavy accumulation of iron within cells. The cells represented here constituted both parenchymal and Kupffer cells.

pigmented casts. The iron stain accentuated these features. The adrenals showed considerable accumulation of hemosiderin within the cells of the zona glomerulosa and zona fasciculata and an associated atrophy.

Case 3.—A white man aged 42 years noticed the first symptoms of his illness four years before his death. During army drill aching pains in the neck and pronounced dyspnea developed. He was found to be severely anemic. The anemia failed to respond to liver and iron therapy.

He was first observed in this hospital two months later. The spleen and liver were not palpable. There was no history of drug sensitivity. The hematologic data (table 3) were compatible with the diagnosis of aplastic anemia. Blood transfusions (500 cc. each) were given approximately every three weeks, and the hemoglobin level was maintained near 10 Gm. per hundred cubic centimeters. The anemia persisted, but for two years the only other abnormality was the presence of scaly, reddish purple lesions of the skin over the malleoli and shin.

TABLE 3.—*Initial and Follow-Up Hematologic Data on Case 3*

Day	Blood, Cc.	Red Blood Cell Count	Hemoglobin, Gm./100 Cc.	Hematocrit, Percentage	Mean Corpuscular Volume, Cu. μ Mean Corpuscular Hemoglobin, γγ Mean Corpuscular Hemoglobin Concentration, Cc./100 Cc.	Reticulocytes, Percentage	Icterus Index	Stool Urobilinogen, Mg./100 Cc.	White Blood Cell Count per Cu. Mm.	Polymorphonuclear Cells, Percentage	Platelets per Cu. Mm.	Temperature Pulse Respirations
1942												
1	.....	3.3	10.15	26.5	80.3 30.7 38	0.4	..	...	4,000	42	200,300	....
55	8,000	2.19	6.25	....	....	3.4	..	...	.....	57	.....	....
1943												
124	.....	2.7	8.85	24	87 32 36	3.2	..	...	4,500	58	.....	....
420	.....	2.4	7.2	....	....	1.6	..	...	4,300	60	.....	....
1944												
780	10,500	2.09	6.9	....	....	1.8	..	...	5,200	49	297,000	....
1945												
832	.....	2.45	8.5	....	....	0.4	51	418	.....	..	.....	....
849	.....	1.8	4.65	....	....	...	44	240	3,100	48	.....	99 80 20
872	22,500	4.2	12.3	....	....	...	46	283	.....	..	51,000	98.6 85 18
1946												
1,172	.....	3.7	11.1	....	....	0.1	..	...	2,100	..	75,200	98 75 18
1,475	.....	3.3	9.5	....	(Splenectomy)	..	..	...	1,100	18	52,900	101.4 90 20
1,488	.....	2.2	8.2	....	....	...	..	...	450	18	.....	103.2 110 24
1,493	16,000	...	9.75	....	....	...	..	...	150	25	76,780	101 130 20

The second hospitalization occurred two and a quarter years later. The presence of jaundice, nausea, malaise and depressed hepatic function (sulfobromophthalein, 75 per cent retained after forty-five minutes; reaction to hippuric acid test, 50 per cent of normal; galactose tolerance test, 6.5 Gm. excreted in five hours) was compatible with a diagnosis of acute hepatitis, probably homologous serum type. After six weeks the patient was discharged improved. Blood transfusions became necessary every two weeks after this time.

One year later, in association with fever (103 F.), cough and malaise, roentgenologic examination of the chest demonstrated evidences of pneumonitis in the left mid-lung field. Penicillin was given, and the patient was discharged improved after fourteen days.

Three months later the anemia continued. The skin was brown (pigmentation). It was decided to perform a splenectomy in an attempt to decrease the required number of transfusions. The anemia remained unaltered. Transfusions were still given once weekly. The sulfobromophthalein test showed 50 per cent retention after one hour. The urea clearance was 64 per cent of normal. The phenolsulfonphthalein test showed a 20 per cent excretion in one hour.

The patient continued to be weak and anemic, and he complained of backache. Bleeding from the gums and intestinal tract developed. Terminally fever developed, and he became weak and died quietly.

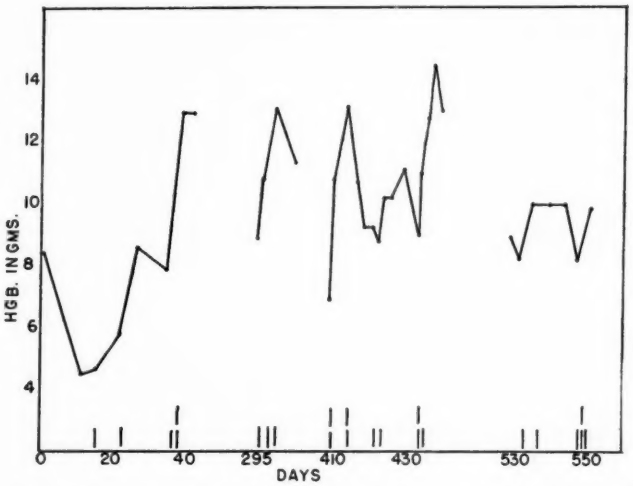

Fig 6.—The peripheral hemoglobin concentration in case 3 is shown. The inability of transfusion therapy to sustain the hemoglobin concentration over prolonged periods is demonstrated. The anemia was frequently severe. Transfusions during hospitalization only are indicated.

Findings at Autopsy.—By request of the mother the autopsy was not performed until twenty-four hours after death.

Gross Examination: There were multiple petechiae of the skin. The heart (weight, 220 Gm.) was flabby. The lungs (right, 740 Gm.; left, 600 Gm.) had crepitant upper lobes and edematous lower lobes. There were multiple small hemorrhages in the left lung. The liver (weight, 1,820 Gm.) was foamy (autolysis). The pancreas was green and had ill defined lobules. The kidneys (right, 220 Gm.; left, 290 Gm.) were similar. The capsule stripped easily, and the surface was smooth. Scattered over the cut surface were many small, firm, gray foci measuring 1 to 2 mm. in size. The right pelvis was hemorrhagic. The urinary bladder contained 150 cc. of bloody urine. The gastrointestinal tract was not remarkable. The visceral

lymph nodes were reddish brown. The brain (weight, 1,190 Gm.) displayed a flat subarachnoid hemorrhage on the inferior surface of the left temporal lobe.

Microscopic Examination: The myocardial fibers were markedly atrophic, and the polar pigment was prominent. In the interstitial area there were frequent foci containing round cells (chronic interstitial myocarditis). The lungs demonstrated moderately thickened and fibrous alveolar walls that contained scattered round cells (chronic pneumonitis). The reticulum was increased. An iron stain showed prominent iron deposits in the fibrous tissue. A recent hemorrhage was noted. There was prominent destruction of the liver. The lobular centers were collapsed and contained many pigment-laden cells. The pigment was as prominent in parenchymal cells as in Kupffer cells. An iron stain showed the major portion of the iron to be at the periphery of the lobules. In the portal areas there was a slight increase in connective tissue and an accumulation of round cells. The kidneys displayed a focal

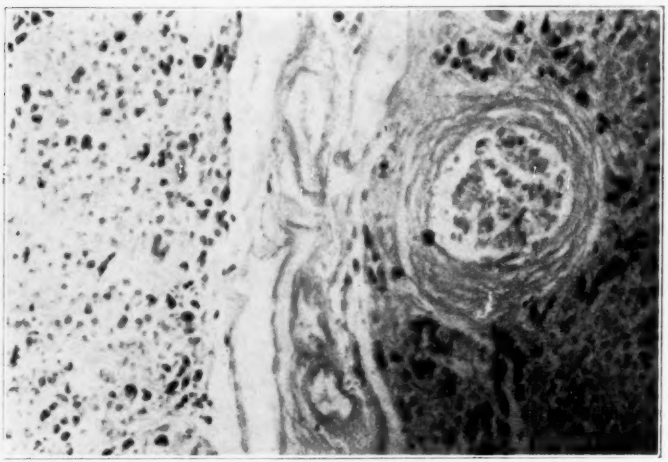

Fig. 7 (× 50; iron stain).—Section of pancreas from case 3. Note the heavy accumulation of iron both in acinar cells and in the moderately increased interstitial tissue.

granulomatous inflammation with a tuberculoid pattern. These foci had necrotic centers which were surrounded by epithelioid cells, giant cells and lymphocytes. Here many yeastlike forms were seen (round bodies and short mycelial forms). There were also diffuse collections of lymphocytes in the stroma. The tubules displayed a moderate hemosiderin accumulation at all levels. Focal recent hemorrhages were seen. The pancreas was the seat of notable hemosiderin pigmentation of the parenchyma and slight interstitial fibrosis. The islet tissue appeared to be preserved. The adrenal glands revealed moderate cortical atrophy and an increase in the pigmentation of all layers. The pituitary had a slight pigment content. A lymph node had a hyalinized tubercle in the cortex. Prominent reticuloendothelial hyperplasia and a heavy degree of intracellular hemosiderin deposits were observed in the medulla.

CASE 4.—A white woman, aged 39 years, gave a history of anemia lasting two and a half years. The anemia was discovered in association with an examination for sudden lumbar pain. There was no response to liver and iron therapy (amounts not known), and weakness continued. Fourteen months before her admission to the hospital the spleen was felt by the patient. During the nine months prior to her admission 27 pints (12.7 liters) of blood had been given. The patient was pale. The main finding was that of a markedly enlarged spleen, which extended beyond the midline and to within 3 cm. of the pelvis. The hematologic data are abstracted in

TABLE 4.—*Initial and Follow-Up Hematologic Data on Case 4*

Day	Blood, Cc.	Red Blood Cell Count	Hemoglobin, Gm./100 Cc.	Hematocrit, Percentage	Mean Corpuscular Volume, Cu. μ Mean Corpuscular Hemoglobin, $\gamma\gamma$ Mean Corpuscular Hemoglobin Concentration, Cc./100 Cc.	Reticulocytes, Percentage	Icterus Index	Stool Urobilinogen, Mg./100 Cc.	White Blood Cell Count per Cu. Mm.	Polymorphonuclear Cells, Percentage	Platelets per Cu. Mm.	Temperature Pulse Respirations
1	500	2,290,000	6.6	22	96 28.8 30	0.3	...	.....	3,100	4	49,500	99.4 100 20
6	2,000	3,500,000	9.15	..	....	...	4.7	988.9	2,750	2	77,650	98.8 75 16
7-12	1,500	4,600,000	12.6	.	....	...	5.6	.....	3,150	4	163,750	99.2 100 22
20-25	500	4,960,000	13.55	..	....	...	...	393	2,150	10	87,000	98.6 90 20
31-37	.....	2,400,000	6.9	..	....	0.4	4.2	652	3,050	9	72,240	98.6 80 20
42	1,000	3,900,000	10.15	37	94.6 27 27	0.2	...	.....	1,900	12	112,500	98.6 85 18
69	500	4,200,000	12	..	....	...	...	.....	1,300	3	110,750	102.6 115 20
72-74	.....	3,900,000	12	..	....	...	...	281	850	2	.....	104.4 125 30
75	500	4,100,000	12.9	..	....	...	...	.....	.....	..	.....	104 140 30

table 4. Sternal marrow could not be obtained after several attempts. A diagnosis of aplastic anemia was made. Soon after the first admission prominent vaginal bleeding developed, and uterine curettage was performed. In an attempt to minimize the transfusion requirements, a splenectomy was performed. The spleen (weight, 1,280 Gm.) demonstrated prominent reticuloendothelial hyperplasia and hemosiderosis.

On the sixth day postoperatively there was a sharp pain in the right lower quadrant of the abdomen, and for ten days the temperature varied between 99 and 101.4 F. Eleven days later there was profuse metrorrhagia. Because of the severe anemia and bone marrow hypoplasia, roentgen ray castration was conducted. For thirty-seven days postoperatively 2,500 cc. of blood was given. Fifty-three days

after splenectomy profuse metrorrhagia and a high fever (101 to 103.5 F.) developed. At the same time there was pain in the right lumbar area. Penicillin failed to alter the course. Severe headaches, nausea and diarrhea developed. Before death jaundice appeared. During this final period, 2,000 cc. of blood was given.

Findings at Autopsy.—Gross Examination: Many petechiae were scattered over the cutaneous surfaces. The heart (weight, 210 Gm.) was not remarkable. The lungs (right, 560 Gm.; left, 450 Gm.) were crepitant throughout except posteriorly, where mild atelectasis existed. Multiple, discrete, firm gray nodules, measuring 2 to 2.5 cm., were present in the upper lobe of the left lung. The splenectomy scar was well healed. Partial intestinal obstruction in the right lower quadrant resulted from a loop of ileum being wrapped about a fibrous band. The liver (weight, 2,440 Gm.) was smooth and a dark greenish brown. On section the lobular markings

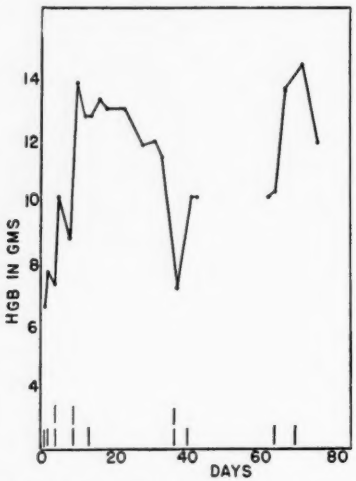

Fig. 8.—The peripheral hemoglobin concentration throughout the course in case 4. Note the similarity of the course to that in case 3.

were distinct and had brown centers and gray peripheries. The gallbladder and bile ducts were normal. The gastrointestinal tract was unaltered in appearance. At the lower pole of the right kidney there was an abscess measuring 0.4 by 1 cm. In the vicinity there were multiple small nodules 1 to 2 mm. in size. The femoral marrow was dry. The brain was grossly normal.

Microscopic Examination: The heart fibers were essentially normal in appearance. There were frequent interstitial collections of round cells and large "myocytes" (focal myocarditis). The lungs demonstrated chronic pneumonitis. The involvement was diffuse. In several sections there was prominent interstitial fibrosis, with collections of lymphocytes, plasma cells and macrophages. In other sections a typical granulomatous inflammation existed, with replacement of the lung structure by fibrous tissue and inflammatory cells. The cells included lymphocytes, plasma cells, numerous macrophages and giant cells. The giant cells frequently contained round yeastlike bodies, some of which showed budding. These structures

were not cultured and completely identified, but they resembled mostly the cryptococcus hominis (Torula). A greater amount of reticulum was observed throughout the lungs. The liver displayed a prominent chronic hepatitis, the portal areas containing many lymphocytes, plasma cells and macrophages. The lobular architecture was well preserved. Acute passive hyperemia and moderate fatty degeneration were present. There was considerable increase in the reticulum of the portal areas. Hemosiderin was prominent within Kupffer and parenchymal cells. An iron stain demonstrated a greater portion of the pigment at the peripheral portions of the lobules. The kidneys were the seat of chronic granulomatous pyelonephritis. There were foci of necrosis and widespread infiltration with lymphocytes, plasma cells and macrophages. Casts in tubules were prominent, and many contained cells of epithelial type. The adrenals were of normal appearance. There was chronic

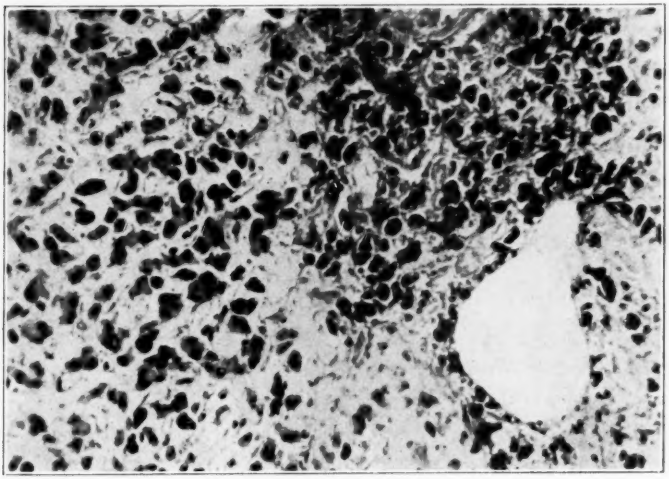

Fig. 9 (× 75; iron stain).—Section of liver from case 4. Note the disorganization of the liver lobule and the heavy accumulation of iron within parenchymal cells.

salpingitis. The brain was normal. One bone marrow smear revealed a yeastlike spherule with a double-contoured margin and a granular center similar to the spherules in the lungs.

Case 5.—A white man, aged 63 years, was admitted to the hospital on five occasions. The first admission occurred nine and a half years before his death. At that time he gave a history of anemia of four years' duration. Three months previously the pallor became marked and was associated with dizziness and tingling of the fingers and toes. The hair was gray and the skin lemon yellow. The hematologic data are given in table 5. A diagnosis of pernicious anemia was made, and liver therapy was given (reticulocyte response, 20 per cent). He was discharged much improved.

He subsequently failed to continue the liver therapy, and three years later he returned with numbness and tingling of the extremities and abdominal aches.

Anemia was prominent and improved on liver therapy (reticulocyte response, 16 per cent).

The third admission occurred one year later, five months after the patient discontinued the liver therapy. Weakness, dyspnea, numbness of the extremities, yellow skin, obesity, an atrophic tongue and an enlarged liver were noted. Pronounced anisocytosis and poikilocytosis were observed. There was histamine

TABLE 5.—*Initial and Follow-Up Hematologic Data on Case 5*

Admission	Day	Blood, Cc.	Red Blood Cell Count	Hemoglobin, Gm./100 Cc.	Mean Corpuscular Volume, Cu. μ	Reticulocytes, Percentage	Icterus Index	White Blood Cell Count per Cu. Mm.	Polymorphonuclear Cells, Percentage	Temperature Pulse Respirations	Miscellaneous
1	1	350	1,080,000	....	118	..	....	4,000	56	100.2 95 20	No free hydrochloric acid; Kline, Kahn and Wassermann tests gave negative reactions
	4	...	2,240,000	8.0	...	12	....	.....	..	100.2 95 18	
	7	350	.....	....	...	20	....	.....	..	98.6 85 20	
	9	...	3,300,000	....	...	..	....	5,000	46	98.6 80 20	
2	1-2	500	3,400,000	10.2	120	..	12.5	5,000	52	99 80 18	Negative reactions to Kline, Kahn and Wassermann tests
	4	400	3,500,000	11.2	...	15	....	.....	..	98.6 75 18	
	10	...	4,300,000	13.7	...	..	....	7,200	56	98.6 75 18	
3	1	1,000	1,800,000	6.6	...	..	....	4,350	57	....	No free hydrochloric acid
	8	...	3,400,000	11.4	...	..	....	.....	..	....	
4	17-18	...	4,150,000	12.6	98	2.3	....	3,550	68	....	
5	1-2	...	3,400,000	10.8	131	3.2	13.2	5,400	69	99.8 88 20	
	12	500	.....	11.5	...	1.2	16	.....	..	98.6 80 18	

achlorhydria. The anemia was severe, but it improved after a transfusion of 1,000 cc. of blood and liver therapy.

The patient was again admitted five and a half years later. Glycosuria had been first noted two years before on a routine examination. Mental changes were noted six months before the admission and included memory changes, lowered concentration, regressed behavior and tremors. The patient was obese and incoherent and had an apical systolic murmur, moderate enlargement of the liver and spleen, edema and brown pigmentation of the lower extremities. There were anemia, leukopenia and the following evidence of hepatic insufficiency: The sulfobromophthalein test

showed 50 per cent retention in 45 minutes, the cephalin flocculation test a 3 plus reaction and the glucose tolerance test a fasting level of 167 mg. per hundred cubic centimeters, which after 1 hour was 258 mg., after 2 hours 250 mg. and after 3 hours 244 mg. The plasma protein concentration was 7.3 Gm. per hundred cubic centimeters, with 4.9 Gm. of globulin. The diagnosis was pernicious anemia and cirrhosis of the liver.

The final admission occurred two and a half months later. Evidence of advanced hepatic insufficiency persisted. The icterus index was 23 and the serum globulin concentration 6.3 Gm. The anemia was not severe at this time. Death occurred after a comatose period.

Findings at Autopsy.—Gross Examination: The skin was yellowish brown everywhere except below the knee, where it was deep brown (pigmentation). There was 4,000 cc. of straw-colored ascitic fluid. The heart (weight, 450 Gm.) was dark brown. The lungs (right, 410 Gm.; left 350 Gm.) were similar. The lower lobes were 40 per cent collapsed, and the upper lobes were gray and had emphysematous bullae. The liver (weight, 1,220 Gm.) had a rough and nodular cirrhotic surface (Laennec's cirrhosis). On section it was deep brown and partitioned by fibrous bands into roundish nodules. The spleen (weight, 640 Gm.) was firm and reddish brown. The pancreas (weight, 160 Gm.) was of normal appearance. Esophageal varices were demonstrable. The kidneys (both weighing 240 Gm.) were similar. The capsule stripped readily, and the surface was smooth. The cut surface was reddish brown, and the vascular markings were prominent. The adrenals were normal. The brain (weight, 1,290 Gm.) appeared normal. Perles' test for iron gave a strongly positive reaction in the liver and pancreas.

Microscopic Examination: The myocardial fibers were normal except for a moderate increase of the pigment at the nuclear poles. Two lung sections were normal, and two sections showed a slight fibrous thickening of the alveolar wall but no prominent pigment collections. The liver had the typical appearance of portal cirrhosis (Laennec's type). Round lobules were surrounded by dense fibrous tissue. There was much hemosiderin within parenchymal cells and Kupffer cells and in the bile duct epithelium. Definite proliferation of bile ducts had apparently occurred, and in the vicinity there were lymphocytes and plasma cells. An iron stain showed a prominent increase in the iron content. The iron was irregularly distributed. The reticulum was markedly increased. The pancreas showed slight fibrosis and the accumulation of a moderate amount of hemosiderin pigment within parenchymal cells and in the connective tissue. The kidneys displayed a prominent number of hyalinized glomeruli (20 per cent of all glomeruli seen). There were focal scars with round cells and hyalinized glomeruli. The epithelium was granular. An iron stain showed a moderate amount of iron in the cells of the proximal segment. Lymph nodes displayed pronounced hyperplasia and many macrophages laden with hemosiderin within the sinuses.

IRON CONTENT OF THE TISSUES

The iron concentration of the liver, pancreas, kidneys and lungs was determined in accordance with the iron technic used by Moore and his co-workers.[1] The determinations were performed on formalde-

1. Moore, C. V.; Arrowsmith, W. R.; Quilligen, J. J., and Read, J. T.: Studies in Iron Transportation and Metabolism: I. Chemical Methods and Normal Values for Plasma Iron and "Easily Split-Off" Blood Iron, J. Clin. Investigation **16**:613-626, 1937.

hyde-fixed tissues, and the results were compared with the iron concentration determined on the same type of tissues from 10 cases of sudden death in which there was no apparent abnormalities of these tissues. In both series all samples were similarly treated. In table 6 the results are expressed as milligrams of iron per hundred grams of tissue. Table 7 reveals the computed total liver iron content (i. e., concentration multiplied by weight)[2] as compared with the total amount of iron introduced in the total amount of blood known to have been given (blood considered as having 50 mg. of iron per hundred cubic centimeters).

It became apparent that the iron content of the tissues was much greater than that normally encountered, which substantiated chemically what was observed grossly and microscopically. Of interest was the preponderant concentration of iron in the liver (the spleens were not studied, as splenectomy had been performed in 4 cases). There was also a substantial increase in the iron content of the other organs studied.

TABLE 6.—*Iron Concentration Expressed as Milligrams per Hundred Grams of Tissue*

Specimen	Liver	Pancreas	Kidney	Lung
Normal Patients				
1	10.04	6.32	5.17	4.42
2	24.08	4.44	10.00	17.75
3	21.41	6.24	11.03	11.77
4	16.22	10.13	10.28	16.19
5	21.36	8.84	14.02	19.3
6	10.93	9.05	12.24	7.65
7	21.01	4.75	4.43	8.77
8	8.68	9.46	11.16	13.92
9	17.44	7.39	11.05	14.29
10	14.86	7.14	11.13	14.62
Average	16.6	7.37	10.16	12.87
Cases				
1	967.46	105.38	94.48	81.94
2	869.68	.....	77.46	71.51
3	573.33	678.0	45.85	74.96
4	162.86	.....	16.91	39.05
5	241.93	62.29	35.92	15.99

The total amount of liver iron in 4 cases approximated the total amount known to have been given in the transfused blood. But a preponderance of iron was also observed elsewhere in the body. It follows that an additional source for iron is needed to explain the

2. The liver was weighed in the fresh state. It was observed on 10 samples that after weeks of formaldehyde fixation a given fresh mass of liver lost an average of 7.1 per cent of its weight. In table 7 this correction was made on the fresh liver weights.

extent of the overload. Absorption by the intestinal mucosa despite an already existing excess seems the most likely explanation.

COMMENT

Certain Aspects of Iron Metabolism.—The total body iron content of an average adult (70 Kg.) is given as near 4.5 Gm.[3] Of this amount, about 55 per cent is incorporated in the hemoglobin molecules within erythrocytes and some 20 per cent is distributed among iron stores, the main store being the liver. The remainder of the iron is distributed between muscle hemoglobin (8 to 10 per cent) and "parenchyma iron" or iron in cytoplasmic enzymes. The low daily iron requirement, 4 to 15 mg.,[4] indicates an efficient normal conservation with the narrow cycle of hemoglobin metabolism: hemoglobin ⟶ serum iron ⟶ bone marrow ⟶ hemoglobin.[3b]

It is agreed that iron is absorbed by the gastrointestinal mucosa, mainly the duodenal mucosa, and in the human being as the reduced ferrous form.[5] The control of the absorption mechanism remains a moot question. Granick[6] has advanced the concept of ferritin formation by the mucosal cells as a basis for this mechanism. Apoferritin, a protein, is considered to be formed by the mucosa. The combination of apoferritin and iron into a protein-iron complex constitutes the ferritin. Ferritin in the mucosal cells is considered to be in equilibrium with the plasma iron. By this concept, as the plasma iron is lowered the mucosal ferritin gives up iron to the plasma and subsequently iron from the bowel enters the mucosa. An increase in the plasma iron is considered to block the mucosal uptake of iron from the bowel.

The total efficiency of the mucosal block in protecting the body from excessive iron absorption has been questioned.[7] It is becoming

3. *(a)* Wintrobe, M. M.: Clinical Hematology, ed. 2, Philadelphia, Lea & Febiger, 1946. *(b)* Laurell, C. B.: Studies on the Transportation and Metabolism of Iron in the Body, with Special Reference to Iron-Binding Component in Human Plasma, Acta physiol. Scandinav. (supp. 46) **14**:1-129, 1947.

4. Heath, C. W., and Patek, A. J., Jr.: The Anemia of Iron Deficiency, Medicine **16**:267-350, 1937.

5. Moore, C. V.; Dubach, R.; Minnich, V., and Roberts, H. K.: Absorption of Ferrous and Ferric Radioactive Iron by Human Subjects and by Dogs, J. Clin. Investigation, **23**:755-767, 1944.

6. Granick, S.: Protein Apoferritin and Ferritin in Iron Feeding and Absorption, Science **103**:107, 1946.

7. Rubach, R.; Callender, S. T. E., and Moore, C. V.: Studies in Iron Transportation and Metabolism: VI. Absorption of Radioactive Iron in Patients with Fever and with Anemias of Varied Etiology, Blood **3**:526-540, 1948. Greenberg, G. R.; Ashenbrucker, H.; Lauritsen, M.; Worth, W.; Humphreys, S. R., and Wintrobe, M. M.: Anemia of Infection: V. Fate of Injected Radioactive Iron in the Presence of Inflammation, J. Clin. Investigation **26**:121-125, 1947.

apparent that in certain conditions in which excessive body iron exists absorption via the bowel may continue. The condition of hemachromatosis has for some time illustrated inefficiencies in the "mucosal block" mechanism. The absence of normal avenues for iron excretion lends the main emphasis to the mucosal mechanism. Should absorption not be properly controlled, flooding of the tissues with iron in time becomes possible in the event ingestion of iron is maintained.

Iron within iron stores occurs in at least two forms, as hemosiderin and as ferritin.[8] Finch and Rath,[9] in studying this feature, have pointed out that only hemosiderin takes up stains in the tissues. An iron stain, therefore, does not depict the entire local iron picture. Both of these iron forms are apparently available for utilization in the hemoglobin metabolism.[10]

The transport iron (plasma or serum iron) has a mean concentration of 120 micrograms per hundred cubic centimeters (range 80 to 200 micrograms). Since the total plasma iron amounts to about 4 mg. and the daily hemoglobin catabolic-anabolic cycle involves 25 mg. of iron, the transport system must be extremely effective.[3b]

The plasma iron concentration at any moment signifies the equilibrium between the destruction and new formation of hemoglobin. An increased plasma iron concentration is expected whenever red blood cell destruction is greater than its production (hemolytic crisis, pernicious anemia, polycythemia, treated aplastic anemia and lowered bone marrow volume).[3b] An increased plasma iron concentration has also been noted in the early phases of hepatitis and after the administration of iron. A decreased plasma iron concentration is expected whenever red blood cell production is greater than its destruction (anemia during regeneration). A lowered level has also been noted in association with inflammation,[11] after loss of blood and during pregnancy.

The plasma iron is bound to protein [3b] (B globulin [12] or fraction IV [13]). Normally an excess of binding protein is present in the

8. Cartwright, G. E.: Dietary Factors Concerned in Erythropoiesis, Blood **2**:256-298, 1947.

9. Rath, C. E., and Finch, C. A.: Sternal Marrow Hemosiderin, J. Lab. & Clin. Med. **33**:81-86, 1948.

10. Cartwright.[8] Rath and Finch.[9]

11. Cartwright, G. E.; Lauritsen, M. H.; Jones, P. J.; Merrill, I. M., and Wintrobe, M. M.: The Anemia of Infection: I. Hypoferremia, Hypercupremia and Alterations in Porphyrin Metabolism in Patients, J. Clin. Investigation **25**:65-80, 1946.

12. Schade, A. L., and Caroline, L.: Raw Hen Egg White and the Role of Iron in Growth Inhibition of Shigella Dysenteriae, Staphylococcus Aureus, Escherichia Coli and Saccharomyces Cerevisiae, Science **100**:14-15, 1944.

13. Schade, A. L., and Caroline, L.: An Iron-Binding Component in Human Blood Plasma, Science **104**:340-341, 1946.

plasma, giving a normal possible upper limit of bound iron near 300 to 350 micrograms per hundred cubic centimeters. This limitation in iron-binding properties has been designated as the "break mechanism" [14] or the "saturation limit." [3b] When the binding capacity is exceeded, the iron escapes rapidly from the circulation.[15] A rapid rise of the plasma iron beyond the binding capacity has been observed to produce ill effects characterized by swelling of nasal mucosa, sneezing, flushing, headaches and abdominal ache.

General Comment.—The cases herein reported are unique and pose several problems. In each instance there were excessive iron deposits throughout the body (iron overload). Attempts to explain all the observed abnormalities on the basis of the known aspects of iron metabolism encounter some difficulties.

The 5 cases include three different types of severe anemia. There are 2 instances of acquired hemolytic anemia that failed to respond to splenectomy. In 2 cases the picture of "aplastic anemia" was present. One patient had a definite pulmonary fungus granuloma demonstrated by tissue sections, and the other patient had a tuberculoid granulomatous nephropathy and was found to have widespread fungus overgrowth twenty-four hours after death. Whether the latter constituted an agonal invasion related to the renal granuloma could not be decided. The fifth case was one of classic pernicious anemia with repeated relapses due to failure of the patient to maintain liver therapy.

Each of these types of anemia has been demonstrated to be associated with an increased plasma iron concentration [3b] and with some increase in the tissue iron content. In these instances the tissue iron content, however, was greatly increased and was of the magnitude ascribed to hemochromatosis. It follows that either the intestinal mucosa allowed iron absorption in the face of an existent iron excess or that the blood transfusions constituted the source of the excess iron.

It is apparent that blood transfusions, by by-passing the mucosal absorption mechanism, afford a rich source of excess iron (0.25 Gm. per pint). Nevertheless, it is just as apparent in these patients that the total iron content of the infused blood did not account for the total amount of iron overload observed (table 7). In cases 1, 2 and 5 the amount of infused iron seemed to account only for the liver iron content. The excessive iron deposited in other tissues requires an

14. Waldenstrom, J., cited by Laurell.[3b]

15. Goetsch, A. T.; Moore, C. V., and Minnich, V.: Observation on the Effect of Massive Doses of Iron Given Intravenously to Patients with Hypochromic Anemia, Blood **1**:129-142, 1946. Greenberg, G. R.; Ashenbrucker, H.; Lauritsen, M., and Wintrobe, M. M.: The Anemia of Infection: IV. The Lack of Relationship Between the Diversion of Iron from the Plasma and the Origin of the Anemia, J. Clin. Investigation **26**:114-120, 1947.

explanation. Since the patients received oral iron therapy during part of their illness and since the dietary intake throughout most of the illnesses was adequate, it appears that absorption of iron via the mucosa ocurred despite an already existing excess of iron. This explanation has obvious implications.

The extent of damage resulting specifically from the iron overload is difficult to assess. The iron pigment, hemosiderin, was observed not only within reticuloendothelial cells of the liver, lymph nodes and bone marrow (splenectomies had been performed in 4 cases) but also within the cytoplasm of parenchymal cells of the liver, kidney and adrenals and in bile duct epithelium and pulmonary parenchyma. In the lung the interstitial fibrosis was prominent. In the liver excessive damage occurred in 3 to 5 cases. The kidneys contained iron casts and displayed clinical evidence of functional impairment. Yet factors other than iron overload per se may have been equally influential in causing these abnormalities.

TABLE 7.—*Computed Total Liver Iron Compared to Amount Given in Transfusions*

Case	Liver Iron, Gm.	Known Amount of Transfusions, Pints	Iron in Blood Given, Gm.
1	21.6	99 (46.9 liters)	24.75
2	17.55	58+ (27.4 liters)	14.50
3	9.7	114 (54 liters)	28.5
4	3.7	16 (7.5 liters)	4.0
5	2.75	12 (5.6 liters)	3.0

In the lungs pneumonitis accompanied the fibrosis, and pneumonitides have varied origins. Hepatitis occurred in cases 2, 3 and 4. The likelihood of homologous serum hepatitis cannot be excluded. The centrolobular damage in the first 2 cases is compatible with the latter. The moderate renal insufficiency (azotemia, casts, albuminuria and depressed clearances)might be blamed in part on the severity of the anemia. One, therefore, has recourse to explanations other than iron deposits for the observed findings. Despite these additional possibilities, it would seem that the excessive intracellular iron deposits should have adverse functional as well as morphologic implications.

It is of interest that in the patients (first 3) receiving numerous transfusions frequent reactions to seemingly compatible blood subsequently developed. At times it became difficult to procure compatible donors. Induced isoimmunization explains this irregularity. Such an explanation would also account for the developed acceleration in the dissipation of infused blood and the need for shortening the interval between transfusions.

The relationship of these cases to conventional hemochromatosis is not easy to appraise. In reviewing the subject of hemochromatosis,[16] one is impressed with the variations which have existed in reported cases. Sheldon [16a] championed the single entity concept of hemochromatosis and presented strong arguments against the idea of blood destruction as the source of the excess iron. Others [17] have failed to produce the picture of hemochromatosis experimentally by the excessive injection of iron salts or hemoglobin solutions. Herbut and Tamaki [18] apparently were able to produce it experimentally by coupling hepatic and pancreatic damage with an excessive iron intake. The more frequent occurrence of hemochromatosis in aplastic anemia has been emphasized.[19]

In general, a great deal of lattitude has been given to the criteria establishing the diagnosis of hemochromatosis. The one central theme has been iron excess, but additional abnormalities have varied in their frequency. Thus the cases herein reported have several prominent features of hemochromatosis. Whether the condition in these should be considered as a type of hemochromatosis is problematic. In 4 cases (1, 3, 4 and 5) accurate accounts of the volume of blood infused throughout the illnesses were available. The observation that the iron intake from the blood transfusions did not seem to account for the entire extent of the iron overload indicated a relationship between these cases and conventional hemochromatosis.[20]

The data herein presented indicate the need for guarding the patient with a "refractory" [21] type of anemia. The indications are

16. (*a*) Sheldon, J. H.: Haemochromatosis, New York, Oxford University Press, 1935. (*b*) Butt, H. R., and Wilder, R. M.: Hemochromatosis: Report of Thirty Cases, Arch. Path. **26**:262-273 (July) 1938. (*c*) Goshell, J. F.; Sladden, A. F.; Wallis, R. L. M., and Vaile, P. T.: A Contribution to the Study of Bronzed Diabetes, Quart. J. Med. **7**:129-152, 1913. (*d*) Cain, J. C.: Hemochromatosis: Report of Six Cases, Texas State J. Med. **36**:356-363, 1940.

17. Muir, R., and Young, J. S.: The Relation of the Liver to the Disposal of Hemoglobin, J. Path. & Bact. **35**:113-125, 1932. Rous, P., and Oliver, J.: Experimental Hemochromatosis, J. Exper. Med. **28**:629-644, 1918.

18. Herbut, P. A., and Tamaki, H. T.: Cirrhosis of the Liver and Diabetes as Related to Hemochromatosis, Am. J. Clin. Path. **16**:640-650, 1946.

19. Zeltmacher, K., and Bevans, M.: Aplastic Anemia and Its Association with Hemochromatosis, Arch. Int. Med. **75**:395-403 (June) 1945.

20. While this was being compiled, an article by Schwartz and Blumenthal entitled "Exogenous Hemochromatosis Resulting from Blood Transfusions" (Blood **3**:617-640, 1948) appeared. These authors reviewed the various aspects of this subject. The iron concentration of various tissues was not reported. Five cases were presented, and 8 others from the literature were reviewed. Thus the present 5 cases appear to bring the number reported in this manner to 18.

21. Bomford, R. R., and Rhoads, C. P.: Refractory Anemia, Quart. J. Med. **10**:175-234, 1941.

that the development of blood banks and consequently the ease of realizing prolonged transfusion therapy have improved the comfort and extended the longevity of these patients. Under such therapy, however, the eventual outcome does not appear bright. The development of isoimmunization of milder types leads to a shorter and shorter span for the infused erythrocytes. The greater frequency of transfusions means that more iron is being deposited throughout the body. Either as a result of the iron excess or because of a lowered resistance to infectious agents or as a result of agents administered with the blood and perhaps other factors, damage occurs throughout the viscera. The extreme iron deposits in reticuloendothelial elements may act to produce the effects of a reticuloendothelial block and thus lower the resistance to infectious agents. Significant alterations have included pulmonary fibrosis and emphysema, hepatitis and extensive hepatic damage, damage to the suprarenal cortex and nephropathy with clinical evidence of renal insufficiency. The patients described here had a fluctuating febrile course. They had complained frequently and had obviously been in poor health.

The first 2 patients had classic hemolytic anemia, apparently of acquired type, that failed to respond to splenectomy. The hemolytic process persisted. There seemed to be no choice save to attempt to maintain life by transfusions. This approach failed. A most intense type of jaundice and iron overload developed. The second 2 patients had the picture of aplastic anemia. The bone marrow was empty of the usual hemopoietic elements. Instead there were groups of lymphocytes, few plasma cells and macrophages (histiocytes). One patient had extensive granulomatous inflammation of the lungs and kidneys. In the lungs many yeast forms resembling Cryptococcus hominis (Torula) were encountered in the tissues. In aspirated bone marrow one such yeast form was encountered. The other patient likewise displayed a granulomatous inflammation of the kidneys. Yeast forms were seen in the center of the tuberculoid lesions but had also overrun the body. Naturally one wonders if such inflammation preceded or followed the hematologic picture. The frequence of the picture of hemochromatosis in "aplastic" anemia has been emphasized by Zeltmacher and Bevans.[19] The fifth case is unique in that portal cirrhosis occurred in a patient with iron overload associated with pernicious anemia. Portal cirrhosis has been considered uncommon in these circumstances.[22]

22. Yates, J. L., and Thalhimer, W.: Treatment of Pernicious Anemia: A Patient Who Received One Hundred and Thirteen Transfusions, J. A. M. A. **87:** 2156-2157 (Dec. 25) 1926. Muir, R., and Dunn, J.: Iron Content of Organs in Bronzed Diabetes, J. Path. & Bact. **19:**226-238, 1914.

In all these instances the blood transfusion seems to have aggravated a tendency toward iron overload. There is a good possibility that the removal of the spleen increased the iron load to the liver and other tissues. This is plausible, since the spleen may act as an additional buffer in taking up iron.

SUMMARY AND CONCLUSIONS

1. Five cases of iron overload of the tissues ("hemosiderosis") aggravated by blood transfusions have been presented.

2. Widespread tissue damage was noted, and factors which may account for this are discussed.

3. The outlook for patients that are sustained hematologically by prolonged blood transfusion therapy does not appear good. Two complications seem likely to develop: (*a*) frequent reactions to the infused blood, with a more rapid dissipation of the infused erythrocytes and (*b*) iron overload of body tissue, mainly the liver.

CONCURRENT HERPES ZOSTER AND CHICKENPOX

Report of a Case

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THE RELATIONSHIP between herpes zoster and chickenpox was first pointed out by von Bókay,[1] of Budapest, in 1888, when he reported cases of the latter disease in members of two families after episodes of herpes zoster in other members. Since then, there has been a growing interest in the subject, especially in the foreign literature. For example, Le Feuvre,[2] in 1917, found in the literature 37 cases of chickenpox after exposure to herpes zoster (shingles) and added 4 cases of his own, making a total of 41 cases. He also reported the converse, 5 cases of herpes zoster after exposure to chickenpox. Moreover, he summarized the reports of 4 cases, which had been noted in the British literature between 1913 and 1916, of concurrent herpes zoster and varicella. In all these cases, the chickenpox followed the herpes zoster after an interval of two to four days. Le Feuvre concluded that the two eruptions represent different phases of the same disease and advised that herpes zoster be made a quarantinable disease, to prevent the development of chickenpox in persons contacted by patients.

More recently, reports of cases in which the two diseases appeared concurrently have appeared in the Argentine [3] and the Spanish [4] literature. Sharpe,[5] in 1946, reported a similar case in a 70 year old man

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1. Von Bókay, J., cited by Horton, S. H., Jr.: Herpes Zoster Following Exposure to Varicella; Treatment of Herpes Zoster with Cowpox Vaccine. U. S. Nav. M. Bull. **48**:742-749 (Sept.-Oct.) 1948.

2. Le Feuvre, W. P.: A Plea for the Recognition of a Common Origin for Shingles and Chickenpox, Brit. J. Dermat. **29**:253-262 (Oct.-Dec.) 1917.

3. Othaz, E. L., and Conti, A. L.: Herpes zona concomitante con varicella (nota clinica), Semana méd. **1**:220-222 (Jan. 29) 1942.

4. Sainz de Aja, E. A.: Simultaneous Chickenpox and Zona: Case, Actas dermo—sif. **36**:445-452 (Feb.) 1945.

5. Sharpe, G. A.: A Case of Concurrent Herpes Zoster and Varicella, Brit. M. J. **1**:916 (June 15) 1946.

and summarized the reports of 7 other cases in the British literature of 1944. All but 2 of these cases were in men of 60 years or over, and the interval between the onset of the two diseases (the chickenpox always following the herpes) was two to seven days.

In the recent American literature, there was a report by Director[6] of the simultaneous occurrence of the two diseases in a 31 year old man. The author pointed out that there is some evidence that chickenpox in childhood makes a person immune to herpes zoster in later life, and that herpes, when it does occur in an adult, represents a partial immunity to the virus of chickenpox in a person who has never become fully immunized by having the disease. This line of reasoning leads to the conclusion that the viruses of chickenpox and herpes zoster must be either identical or very closely related, and the rare cases of the two diseases occurring simultaneously can be explained by increased virulence of the virus, sufficient to overcome the partial immunity to chickenpox.

There is experimental as well as clinical confirmation of the relation between the two diseases. Bedson,[7] citing Netter and Urbain, whose work appeared in the French literature between 1924 and 1926, noted that serums of patients convalescing from varicella gave a positive reaction to the complement fixation test with an antigen prepared from crusts of herpes zoster, as well as with an antigen prepared from crusts of varicella. The converse was also found to be true. Bedson pointed out, however, that the final solution of the relation between the two diseases will depend on the finding of a suitable experimental animal.

Because of the relative rarity of the simultaneous occurrence of the two diseases, we report the following case.

REPORT OF A CASE

S. N., a white woman aged 72, was admitted to Presbyterian Hospital on April 10, 1948, because of herpes zoster of the right side at the level of the eleventh and twelfth thoracic ganglions. There was a florid eruption of coalescent vesicles over the lower portion of the right side of the chest and extending across the right flank to the upper portion of the right side of the abdomen. The patient's illness had begun on April 5, with pain in the lower part of the right side of the chest, and the eruption was first noted about twenty-four hours after the onset of the pain. Aside from the herpes, there were no significant findings on physical examination.

6. Director, W.: Zoster with Varicelliform Eruption: Report of a Case, U. S. Nav. M. Bull. **42**:186-187 (Jan.) 1944.

7. Bedson, S. P., in A System of Bacteriology in Relation to Medicine, Medical Research Council, London, His Majesty's Stationery Office, 1930, vol. 7, pp. 166-167.

On April 11, the patient complained of a severe sore throat, and her temperature was 101 F. Examination of the pharynx showed intense swelling and redness of the uvula and injection of the pharynx, without exudate. Next day the inflammation of the uvula and pharynx was subsiding, and the temperature had dropped to 99 F. A few papules and vesicles were noted on the patient's scalp, face, neck, chest and abdomen. On April 13, the number of these cutaneous lesions had increased tremendously, and some of the vesicles had become pustular, with umbilicated centers. The eruption was entirely typical of chickenpox. The patient had not had that disease before, and there was no history of recent exposure to chickenpox, or of contact with a patient with herpes zoster. The patient was isolated, and the chickenpox was treated symptomatically. By April 20, the generalized eruption of varicella had subsided, and the patient was taken out of isolation.

The herpes zoster, however, ran a protracted course, in spite of roentgen therapy and large doses of thiamine hydrochloride. The cutaneous lesions did not involute until the end of May, almost two months after the onset, and severe pain persisted after that. Beginning on June 25, the patient was given intramuscular injections of 200 mg. of tetraethyl ammonium chloride, with some improvement of the postherpetic pain. She was discharged from the hospital on July 6.

SUMMARY AND CONCLUSIONS

A case of concurrent herpes zoster and chickenpox in a 72 year old woman is reported.

The relation between the two diseases is discussed.

The indications are that the viruses of herpes zoster and of chickenpox are either identical or closely related.

The simultaneous occurrence of the two diseases is presumably due to increased virulence of the virus, sufficient to overcome the patient's partial immunity to chickenpox.

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DISSEMINATED COCCIDIOIDOMYCOSIS AND LYMPHO-HEMATOGENOUS TUBERCULOSIS

Report of a Case

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COCCIDIOIDOMYCOSIS is a fungous disease endemic to large areas of the southwestern United States. Chlamydospores, the infectious "vegetative" form of Coccidioides immitis, enter the body through the respiratory tract and develop into doubly refractile spherules, which reproduce by endosporulation. Infection through the skin is rare but has been reported.[1] The primary pulmonary infection is usually asymptomatic, localized and self limited. The usual course is uncomplicated healing of the primary focus with fibrosis and occasionally cacification. The only evidence of infection may be a positive reaction of the skin to coccidioidin injected intradermally. Dr. Charles E. Smith, in an excellent summary (1947), noted that the initial primary infection is nearly always pulmonary and well focalized. Sixty per cent of infections are asymptomatic and are recognizable only by the development of sensitivity to coccidioidin. Another type produces symptoms of an infection of the upper respiratory tract or of influenza. The fungus may be found in the sputum, and the reaction to the skin tests with coccidioidin becomes positive. A roentgenogram of the chest may reveal a pulmonary lesion (bronchopneumonia), enlarged hilar lymph nodes and occasionally pleural effusion. About 5 per cent of patients have an episode of erythema nodosum or erythema multiforme.

The clinical history and gross pathologic features of coccidioidomycosis are similar to those of pulmonary tuberculosis.[2] Comparative

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1. Kessel, J. F.: Recent Observations on Coccidioides Infections, Am. J. Trop. Med. **21**:447-453 (May) 1941. Rixferd, E., and Gilchrist, T. C.: Two Cases of Protozoan (Coccidioidal) Infection of the Skin and Other Organs, Johns Hopkins Hosp. Rep. **1**:209, 1896.

2. Smith, C. E.: Parallelism of Coccidioidal and Tuberculous Infections, Radiology **38**:643-648 (June) 1942.

roentgenograms may be indistinguishable.[3] The cause of pulmonary lesions is often clarified by the isolation of specific organisms.

Disseminated coccidioidomycosis is a rare complication, occurring once in about 750 cases. Dissemination may occur during the primary infection or later; it is commoner in darker-skinned persons, such as Mexicans, Negroes and Orientals, occurring once in every 40 cases of the infection in male patients. The fatality rate is 50 per cent.[4] The progressive disseminated infection is nearly always manifested within a few months after the initial primary infection, and often with no interlude, as emphasized by Smith.

Clinically, coccidioidomycosis is similar to lymphohematogenous tuberculosis.[5] Lesions develop in the meninges, skin, lymph nodes, bones or joints, or peritoneum. The following case is presented to show similarities and differences in the two conditions. We have been unable to find any other case report of coexisting disseminated coccidioidomycosis and lymphohematogenous tuberculosis in the available medical literature.

REPORT OF CASE

History.—The patient, J. A., was a Japanese-American man of 21. At the age of 5 he had had surgical drainage of empyema of the right side of the chest without sequelae. He had had no other serious illnesses. The patient lived in California and had spent five months in the San Joaquin Valley. In September 1942 he was sent to a relocation camp in Arizona. In November malaise, asthenia, a nonproductive cough and a vesicular eruption of the fingers had developed. The reaction to the skin test with coccidioidin, which had been negative in September, became positive for the first time. The reaction to a skin test with tuberculin, done for the first time, was also positive. The patient's course was complicated by an acute pleurisy of the left side, with effusion. On two occasions, clear, yellow fluid was aspirated from the left pleural cavity. Roentgenograms of the chest were said to have shown a suggestive infiltrate at the apex of the right lung. After four months in a hospital the patient was discharged as asymptomatic, and he returned to work as a wood carver. Ten months later (in January 1944) a swelling appeared over the sternum. The mass soon ruptured painlessly and drained intermittently. In the spring the patient went to New York city; he felt well until July, when he experienced anorexia and a loss of 25 pounds (11.3 Kg.) in weight. For the next five weeks he had frequent frontal headaches on the right side; three palpable nodules soon developed on the scalp. Pain and swelling appeared over the dorsum of the left foot, and he noticed occasional fever. Because of these complaints, he was admitted to the chest service of Bellevue Hospital on August 29.

3. Carter, R. A.: Roentgen Diagnosis of Fungous Infections of the Lungs with Special Reference to Coccidioidomycosis, Radiology **38**:649-659 (June) 1942.

4. Smith, C. E.: Coccidioidomycosis, M. Clin. North America **27**:790-807 (May) 1943.

5. Marple, C. D.: Progressive (Disseminated) Coccidioidomycosis, Ann. Int. Med. **23**:240-249 (Aug.) 1945.

Physical Examination.—On admission the patient appeared well developed and somewhat thin and showed evidence of recent loss in weight. Three small, slightly tender, fluctuant masses were present in the frontal region of the scalp. The cervical, left axillary and inguinal nodes were slightly enlarged, discrete and nontender. The trachea was in the midline. Below the angle of the right scapula was a healed scar of a thoracotomy performed in childhood. Over the left side of the sternum a sinus drained scant, thin, green pus. The lungs were clear on per-

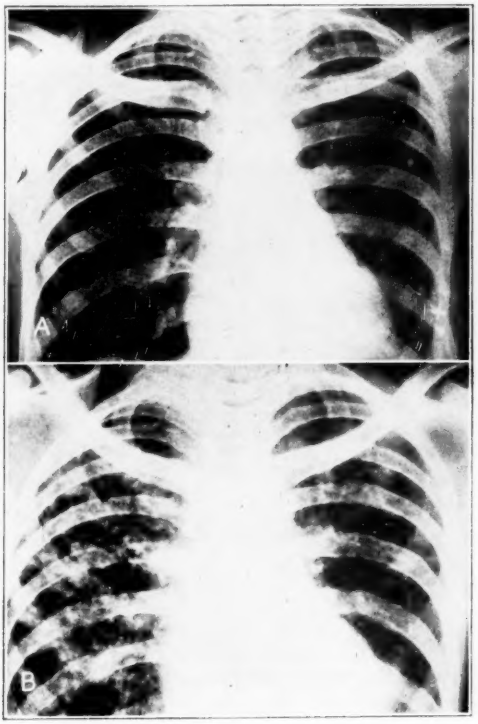

Fig. 1.—Roentgenograms of the patient's chest: *A*, on admission, showing fine, scattered, nodular infiltrations; *B*, six months later, showing dissemination, enlargement and confluence of the lesions.

cussion and auscultation except for slightly impaired resonance with diminished breath sounds over the posterior lateral portion of the base of the left lung. No rales were heard. There was a large, fluctuant swelling over the dorsum of the left foot. Pressure on this swelling and over the metatarsal and tarsal bones caused pain.

Laboratory and Roentgenologic Examination.—The value for hemoglobin was 11 Gm. per hundred cubic centimeters; the white blood cell count was 10,800, and the differential leukocyte count was normal. During his stay in the hospital

the highest white blood cell count recorded was 13,400. The gastric contents showed acid-fast bacilli on direct smear and culture but did not contain C. immitis. Pus aspirated from the abscess of the foot contained the cyst forms of Coccidioides but no acid-fast bacilli. Reactions to skin tests with coccidioidin were repeatedly negative, but became slightly positive after one month of hospitalization. Roentgenograms of the chest on admission (fig. 1 *A*) showed scattered, fine, nodular infiltrations in both lungs. Roentgenograms made at about two week intervals revealed dissemination, enlargement and confluence of the lesions (fig. 1 *B*). Roentgenograms of bone showed three areas of destruction in the skull (fig. 2) and a destructive process in the head and upper end of the left humerus (fig. 3). The left tarsal and metatarsal bones had similar lesions.

Course.—The illness had an irregularly febrile course, with the temperature usually between 100 and 101 F. On several occasions penicillin was instilled

Fig. 2.—Roentgenogram of the patient's skull, showing three areas of destruction.

into each abscess of the scalp after aspiration. Penicillin was also given intramuscularly. The dosage was 15,000 units every three hours, with daily intravenous booster doses, for a total of 2,000,000 units. A total of 30 Gm. of sulfadiazine was then given in nine days. The drugs had no apparent effect. The three abscesses of the scalp were incised and drained reddish brown pus. At the base of each abscess was uncovered skull, and each had in its center a circular area about 1 cm. in diameter, in which the outer table of bone was seen to be necrotic. Actually, both tables of bone were necrotic, and the dura could be felt with a probe in the right frontoparietal area.

Late in December fluctuant masses appeared on the back, the left side of the neck, over the left iliac crest and on the upper part of the left humerus. Pus from these abscesses contained cyst forms of C. immitis but did not yield acid-fast bacilli. The urine, which had been unremarkable previously, now began to show albumin and 20 to 60 white blood cells per high power field. Sulfamerazine U. S. P. was given in a dosage of 1 Gm. every eight hours, for three weeks with

no effect. The patient gradually became weaker, and he died on the one hundred and third day in the hospital (Feb. 27, 1945).

Necropsy.—Necropsy was performed by Dr. David M. Spain, pathologist of the chest service at Bellevue Hospital:

There were three circumscribed shaved areas on the scalp, each with a draining sinus in its center. These extended down through the soft tissue and involved the bone. Each sinus measured 0.5 cm. in diameter. There was a draining sinus in the region of the left shoulder, and the left shoulder joint was swollen to about three times the usual size. The sinus led directly into the

Fig. 3.—Roentgenogram showing destructive process in the head and upper end of the left humerus.

shoulder joint; the base of the joint contained about 100 cc. of cheesy, yellow-green material. There was another draining sinus over the sternum; similar material was discharged from it. This sinus led directly into the sternum. Over the left ankle there were also draining sinuses, which led into the joint and surrounding bone. The eyes, ears and nose showed no gross abnormality. The trachea was in the midline.

Adhesions were present in both pleural spaces. The parietal and visceral parts of the pericardium were adherent to each other. All the abdominal viscera were in their normal relation, but the loops of the intestine were all matted together in one indistinguishable mass. The omentum was plastered down and

adherent to the intestinal mass. The entire peritoneal surface and the omentum and loops of the intestine were studded with innumerable nodules, varying in diameter from 1 to 3 mm.; these were yellowish and fairly firm.

Heart: An adhesive pericarditis was present. Overlying the right side of the heart near the base, at the junction of the atrium and the ventricle, there was a yellowish white plaque of tissue, which extended from the epicardium a short distance into the underlying portion of the myocardium. There was a small plaque of tissue overlying the apex of the heart, but it did not extend into the myocardium. Within these two plaques were small focal areas of necrosis. The remainder of the pericardial surface was dull and opaque. None of the chambers was significantly enlarged or dilated. The valves exhibited no remarkable changes, and the coronary arteries revealed no atherosclerosis.

Lungs: Both pleural cavities were completely obliterated by adhesions, those on the left side being much denser than those on the right. In the right lung all the lobes were involved, and on section grayish to yellowish gray foci were observed, which varied in size from 1 mm. in diameter to areas composing lobules of the lung. In the larger areas numerous millimeter-wide foci were present, as well as areas of greater consolidation. Several of the large areas showed softening of the central portion, which was full of yellowish pus. Scattered foci in the larger areas showed considerable congestion in and around the lesion. A careful search failed to reveal any sizable cavities. On the left side the upper third of both lobes showed a condition similar to that noted on the right side. The lower portion of both lungs contained only relatively few scattered, millimeter-wide, grayish foci. A careful search also failed to reveal any sizable cavities in the left lung. In the apical portion of the upper lobe there was a firm, fibrocaseous focus, approximately 2 mm. in diameter; this was the only lesion observed which suggested an old focus, and it was interpreted as tuberculous.

Lymph Nodes: Section of the hilar and mediastinal lymph nodes revealed involvement of several. Two nodes adjacent to the bronchus of the upper lobe of the left lung showed small spicules of calcification; three nodes situated to the left of the trachea, about 1 cm. above its bifurcation, were firm, approximately 3 mm. in diameter, and on section appeared caseous, and, in addition, an occasional node on either side showed a few pearly gray, millimeter-wide foci. Otherwise, no gross pathologic change was observed except for moderate anthracosis. A survey of both lungs gave the impression that the pathologic state was due to bronchogenic spread. The original focus from which the spread occurred was not determined.

Liver: The liver weighed 1,400 Gm. The capsule was smooth except for nodules, which studded the entire peritoneal surface. The parenchyma cut with the usual resistance, and the lobular architecture was fairly well discerned.

Spleen: The spleen weighed 350 Gm. The capsule was dark purple in color. Immediately beneath the capsule there were three yellowish areas of necrosis, measuring approximately 1 cm. in diameter. The rest of the spleen showed a dark purple pulp. The malpighian bodies were fairly prominent.

Adrenal Glands: The glands were normal in position and size. The cortices were yellow and the medullas showed autolysis.

Kidneys: Each kidney weighed 150 Gm. The upper half of the parenchyma of the right kidney was completely destroyed and replaced with yellowish white tissue, which showed necrosis and small areas of cavitation. The tissue extended

from the cortex down to the pelvis. There was one smaller nodule of necrosis present in the left kidney; there the cortex measured about 1 cm. in diameter. Otherwise, the capsule was stripped with ease, and the remaining portion of the cortex was of normal width and well differentiated from the medulla. The pelves were not dilated, and the ureters were patent.

Prostate Gland: The gland was nodular. On section it presented nodules of necrosis similar to those seen in the kidneys. The areas of necrosis extended into the seminal vesicles, which were greatly enlarged and were observed to be solid masses of grayish yellow tissue.

Gastrointestinal Tract: The mucosa of the esophagus, stomach and duodenum was intact. No significant changes were noted. The remainder of the intestine was matted together, the walls being studded with nodules, but no definite ulceration was observed except in one area in the ileocecal region, where the mucosa appeared to be eroded.

Skull and Brain: The scalp was reflected and the skull removed at autopsy, and it was observed that the sinuses (described previously) led through the entire thickness of the skull. Yellowish, purulent material surrounded, and pressed on each sinus outside the dura but did not extend through it. The brain revealed no significant gross change; it was saved for further study.

Microscopic Examination.—Heart: The epicardium revealed calcification, fibrosis and caseation necrosis. The myocardial fibers were unchanged; no fibrosis was present there.

Aorta: There were no significant changes in the aorta.

Lungs: Both diffuse and focal infiltrations of epithelioid cells, lymphocytes and giant cells were present. Areas of caseation necrosis were scattered throughout, and some fibrosis was present. The stain for acid-fast organisms revealed the presence of bacilli. Coccidioides were present.

Lymph Nodes: Caseation necrosis and fibrosis were present. The stain for acid-fast organisms revealed bacilli. Coccidioides were not seen.

Liver: Sections showed no significant changes except for occasional tubercles.

Spleen: Several large areas of caseation necrosis were present.

Adrenal Glands: Occasional tubercles were present.

Kidneys: Numerous tubercles and areas of caseation necrosis were present. Specific stains for acid-fast organisms revealed bacilli. Coccidioides were not seen.

Bladder: No changes were noted in the bladder.

Prostate Gland and Seminal Vesicles: Large areas of caseation necrosis were present, with tubercle formation. The stain for acid-fast organisms revealed bacilli. Coccidioides were not seen.

Peritoneum: Nodules consisting of caseation necrosis and fibrosis were present. An occasional coccidioidal spherule was seen. The stain for acid-fast organisms revealed bacilli.

Dura: An exudate consisting of caseation necrosis, mononuclear cells and lymphocytes was observed. Numerous coccidioides were present. Specific stains showed no acid-fast bacilli.

Tissue from Sternum: Caseation necrosis was noted. The skin for acid-fast organisms revealed bacilli. Coccidioides were not seen.

Tissue from Shoulder: On section the tissue revealed caseation necrosis and the presence of coccidioides. The stain for acid-fast organisms revealed no bacilli.

Bone Marrow: No abnormalities were noted in the marrow.

Skin: An ulcer was present, the base of which revealed caseation necrosis and tubercles. Specific stains revealed the presence of acid-fast bacilli. No coccidioides were seen.

The final diagnoses were (1) coccidioidomycosis of the lungs, peritoneum, left shoulder joint, left ankle, skull and dura, and (2) tuberculosis of the lungs, hilar lymph nodes, liver, spleen, kidneys, peritoneum, adrenal glands, prostate gland, seminal vesicles, sternum, pericardium and ileum.

COMMENT

The patient was a Japanese-American. He lived in California, where he spent five months in the San Joaquin Valley, and in Arizona; coccidioidomycosis is endemic in both these regions. After one month in Arizona, the patient had a pleurisy of the left side, with effusion and a cutaneous eruption. Reaction to skin tests with coccidioidin became positive. The reaction to the skin test with tuberculin, when done for the first time, was also positive. One might postulate that coccidioidal nodules in addition to suppuration may have activated an old tuberculous focus, so that both the tubercle bacilli and the coccidioides were later disseminated from approximately the same site. (The effect of suppuration on tuberculous pulmonary lesions was thoroughly studied and reported by Baum and Amberson.[6]) Another possibility is that the patient acquired coccidioidomycosis and the primary infection with tuberculosis at about the same time from September to November 1942. Lymphohematogenous spread of primary tuberculosis is not uncommon in persons of darker-skinned races. Similarly, the development of progressive disseminated coccidioidomycosis is not uncommon (the incidence is 1 case in every 40 cases of the infection among darker-skinned male patients).

The first evidence of hematogenous dissemination was the nodule over the sternum, which appeared after the patient had been asymptomatic for ten months after the pleural effusion. Acid-fast bacilli and coccidioidal endospores were carried by the blood stream to various regions of the body. Both organisms grew in the lungs, the omentum and the peritoneum. Only acid-fast bacilli were found in the liver, spleen, kidneys, adrenal glands, prostate gland, seminal vesicles, sternum and pericardium. Only coccidioidal endospores grew in the left shoulder joint, left ankle, skull, dura and subcutaneous tissue. Acid-fast bacilli were present in the sputum; bronchogenic spread may have occurred

6. Baum, O. S., and Amberson, J. B., Jr.: Non-Tuberculous Pulmonary Infections Complicating Pulmonary Tuberculosis, Am. Rev. Tuberc. **45**:243-279 (March) 1942.

in the lungs. The pathologic observations at autopsy were consistent with this theory. The ulcer in the ileum was probably caused by the swallowing of sputum containing acid-fast bacilli.

Scattered destruction of bone and subcutaneous abscesses are frequent in disseminated coccidioidomycosis, whereas involvement of the gastrointestinal tract is practically unknown, probably because the gastric juice destroys the fungus. Forbus and Bestebreurtje,[7] in an excellent study, noted involvement of the following organs at autopsy (the frequencies noted are based on 50 cases of disseminated coccidioidomycosis): lungs, 86 per cent; lymph nodes, 72 per cent; spleen, 70 per cent; skin and subcutaneous tissue, 64 per cent; kidneys, 60 per cent; liver, 60 per cent; pleura, 50 per cent, and bones, 48 per cent. Less frequently affected were the meninges, adrenal glands, myocardium, brain, bronchi, dura, pancreas and pericardium. Other tissues are infected uncommonly, although virtually any part of the body may be involved. This thorough work[7] contains a review of the literature of coccidioidomycosis up to 1946. Neither in the two hundred and thirty-six papers reviewed nor in the 95 cases of disseminated coccidioidomycosis in which autopsy was performed was there any report of coincidental disseminated cocidioidomycosis and disseminated lymphohematogenous tuberculosis. In tuberculosis multiple lesions of bone are uncommon and the skull is invaded rarely. Extensive tuberculous involvement of the genitourinary or the gastrointestinal tract is frequent. These clinical features were present in this case.

The reaction to the skin test with coccidioidin was negative in September 1942 but became positive in November 1942, when the patient noted malaise, asthenia and cough. This was evidently the time of onset of the initial primary coccidioidal infection. Dissemination occurred one year later. Reactions to skin tests with coccidioidin made after dissemination had occurred were negative; later they became weakly positive. Dr. C. E. Smith emphasized that the reaction of the skin to coccidioidin may be much less active with disseminated than with primary infections and may decrease progressively until the patient is anergic terminally.

Dr. Smith noted that dissemination occurred once in 40 cases of primary infection in dark-skinned male patients and only once in 400 cases of primary infection in white male patients. Dissemination occurs only one-fourth to one-half as often in female patients. Dissemination is rare after the infection has become well focalized.

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7. Forbus, W. D., and Bestebreurtje, A. M.: Coccidioidomycosis: A Study of Ninety-Five Cases of the Disseminated Type with Special Reference to the Pathogenesis of the Disease, Mil. Surgeon **99**:653-719 (Nov.) 1946.

SUMMARY

A case of coexisting disseminated coccidioidomycosis and disseminated lymphohematogenous miliary tuberculosis is reported, with autopsy observations. This is believed to be the first such case reported. During life smears and cultures made from aspirated gastric contents showed acid-fast bacilli and smears and cultures of material from the subcutaneous abscess of the foot revealed C. immitis. At autopsy both Mycobacterium tuberculosis and C. immitis were present in the lungs, omentum and peritoneum. Only acid-fast bacilli were found in the liver, spleen, kidneys, adrenal glands, prostate gland, seminal vesicles, sternum and pericardium. Only coccidioides were obtained from the left shoulder joint, left ankle, skull, pleura and abscesses in the subcutaneous tissue.

Acknowledgment is made to J. Burns Amberson, M. D., director, Chest Service, Bellevue Hospital, for his permission to report this case.

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PRESENT STATUS OF INSULIN RESISTANCE

Report of a Case with Autopsy

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INSULIN resistance is a curious clinical phenomenon, the exact etiologic mechanisms of which are as yet unknown. Since marked variations in sensitivity to insulin exist among both diabetic and nondiabetic patients, the term is popularly restricted to patients requiring 200 or more units of insulin daily to lower appreciably the blood sugar content.[1] In terms of diabetic patients, the validity of this definition is enhanced by reports that depancreatized man probably requires only 35 to 50 units daily to control adequately the resultant diabetes.[2]

The term "insulin insensitive" [3] has been suggested to characterize those diabetic patients who require less than 200 units daily but more than usual doses for adequate control.

It is of interest that insulin resistance has been encountered in nondiabetic schizophrenic patients undergoing shock therapy.[4] This renders any theory untenable which demands the coexistence of diabetes

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From the Department of Internal Medicine, Grand Forks Clinic.

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1. Martin, W. P.; Martin, H. E.; Lyster, R. W., and Strouse, S.: Insulin Resistance: Critical Survey of the Literature with the Report of a Case, J. Clin. Endocrinol. **1**:387-398 (May) 1941.

2. Waugh, J. M.; Dixon, C. F.; Clagett, O. T.; Bollman, J. L.; Sprague, R. G., and Comfort, M. W.: Total Pancreatectomy: A Symposium Presenting Four Successful Cases and a Report on Metabolic Observations, Proc. Staff Meet., Mayo Clin. **21**:25 (Jan. 23) 1946. Ricketts, H. T.; Brunschwig, A., and Knowlton, K.: Effects of Total Pancreatectomy in a Patient with Diabetes, Am. J. Med. **1**:229-245 (Sept.) 1946. Goldner, M. G., and Clark, D. E.: The Insulin Requirement of Man After Total Pancreatectomy, J. Clin. Endocrinol. **4**:194-197 (May) 1944. Brunschwig, A.; Ricketts, H. T., and Bigelow, R. R.: Total Pancreatectomy, Total Gastrectomy, Total Duodenectomy, Splenectomy, Left Adrenalectomy and Omentectomy in a Diabetic Patient, Recovery, Surg., Gynec. & Obst. **80**:252-256 (March) 1945.

3. Axelrod, A. R.; Lobe, S.; Orten, J. M.; and Myers, G. B.: Insulin Resistance, Ann. Int. Med. **27**:555-575 (Oct.) 1947.

4. Kalinowsky, L. B.; and Hoch, P. H.: Shock Treatments and Other Somatic Procedures in Psychiatry, New York, Grune & Stratton, Inc., 1946, p. 15. Banting, F. G.; Franks, W. R.; and Gairns, S.: Anti-Insulin Activity of Serum of Insulin Treated Schizophrenic Patient, Am. J. Psychiat. **115**:562-565 (Nov.) 1938.

mellitus in all cases of insulin resistance, although 9 per cent of patients reported on in the literature were in diabetic coma. Furthermore, the statement that insulin resistance is "hyperglycemia, with or without associated ketosis, resistant to, or better, hyporesponsive to the action of insulin" [5] constitutes an inadequate definition in the light of the preceding remarks, because this precludes the phenomenon in nondiabetic patients.

A vast amount of experimental and clinical data has been accumulated in support of various etiologic concepts of insulin resistance.[6] While no single theory is entirely convincing, the total weight of opinion strongly favors multiple causes. Smelo incorporated most of the existing concepts into the following comprehensive classification.[7]

Clinical States Associated With Lack of Response to Insulin

A. Disruption of the functional integrity and innate characteristics of the tissues
   Hemochromatosis
   Recurrent jaundice with calculous common duct obstruction
   Multiple hepatic infarcts

B. Dysfunction of enzyme systems
   Lipoatrophy (lypodystrophy) with hepatic cirrhosis
   Defective hepatic glycogenesis

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5. Smelo, L. S.: Insulin Resistance, Proc. Am. Diabetes A. **8**:77-1115, 1948.

6. Karelitz, S.; Cohen, P. and Leader, S. D.: Insulin Inactivation by Human Blood Cells and Plasma in Vitro, Arch. Int. Med. **45**:546-554 (April) 1930. Wien, R.: The Influence of Fever on the Peripheral Action of Insulin, Quart. J. Pharm. & Pharmacol. **11**:177-185 (April-June) 1938. Best, C. H.; Campbell, J., and Haist, R. E.: Effect of Anterior Pituitary Extracts on Insulin Content of Pancreas, J. Physiol. **97**:200-206 (Dec.) 1939. Young, F. G.: Experimental Investigation of Relationship of Anterior Hypophysis to Diabetes Mellitus, Proc. Roy. Soc. Med. **31**:1305-1316 (Sept.) 1938. Lawrence, R. D., and Buckley, O. B.: The Inhibition of Insulin Action by Toxemias and Its Explanation: I. The Effect of Diphtheria Toxin on Blood-Sugar and Insulin Action in Rabbits, Brit. J. Exper. Path. **8**:58-75 (Feb.) 1927. Zeckwer, I. T., and Evans, C. L.: Nature of Hyperglycemic Response to Injection of Certain Killed Bacteria, Brit. J. Exper. Path. **8**:280-288 (Aug.) 1927. Himsworth, H. P.: The Activation of Insulin, Lancet **2**:935-936 (Oct. 29) 1932. Taubenhaus, M., and Soskin, S.: On the Mechanism of Insulin Resistance in Toxemic States, J. Clin. Endocrinol. **2**:171-175 (March) 1942. Sweeney, J. S.; Barshop, N., and LoBello, L. C.: Effect of Toxemia on Tolerance for Dextrose and on Action of Insulin, Arch. Int. Med. **53**:689-698 (May) 1934. Williams, J. L., and Dick, G. F.: Decreased Dextrose Tolerance in Acute Infectious Disease, ibid. **50**:801-818 (Dec.) 1932. Sweeney, J. S.; Barshop, N.; LoBello, L. C., and Rosenthal, R. S.: Effect of Toxemia on Tolerance for Dextrose and on Action of Insulin, ibid. **54**:381-388 (Sept.) 1934. Hayward, G. W., and Duncan, G. G.: Effect of Alteration in Metabolic Rate on Action of Insulin, Am. J. M. Sc. **198**:396-402 (Sept.) 1939.

7. (*a*) Smelo, L. S.: Lack of Response to Insulin, South. M. J. **40**:333-340 (April) 1947; (*a*) Smelo.[5]

C. Dysfunction of hormonal or nervous system regulation
  1. Insufficiency of insulin
    a. Delayed absorption
    b. Immunologic inactivation or neutralization
      Local or general allergic sensitivity with hormonal resistance
    c. Combination of b. with porphyria
    d. Infections with probable insulin inhibition or destruction
      Pulmonary tuberculosis
      Gangrene and cellulitis of lower limb
      Rheumatoid arthritis
    e. Blood dyscrasias with insulin inhibition
      Chronic lymphatic leukemia
  2. Excess of contra-insulin hormone
    a. Pituitary hyperfunction
    b. Acromegaly
    c. Cushing's syndrome
    d. Hemorrhagic cyst of midbrain
    e. Hyperthyroidism
    f. Pheochromocytoma

D. Pathologic state of etiologic or concomitant significance not present or known

Certain conditions such as allergic states, infections, endocrine dysfunction and hepatic disease seem to bear more than a coincidental relationship. Recently insulin antagonists or neutralizing antibodies have been demonstrated in the serum of certain insulin-resistant patients.[8]

Suffice it to say, then, that the insulin requirement of the diabetic patient is not consistently predicated on quantitative insulin deficiency, but often the extrainsular elements, such as the contrainsular hormones of the anterior pituitary, thyroid and suprarenal glands qualitatively alter insulin to reduce its hypoglycemic potential. Hence, it may be postulated that in some cases diabetes mellitus may itself be due to

8. Lowell, F. C.: Immunologic Studies in Insulin Resistance, J. Clin. Investigation **23**:225-231 and 233-239 (March) 1944. Goldner, M. G., and Ricketts, H. T.: Insulin Allergy: A Report of Eight Cases with Generalized Symptoms, J. Clin. Endocrinol. **2**:595-602 (Oct.) 1942. Hart, J. F., and Vicens, C. A.: Association of Extreme Insulin Resistance with Allergy: Report of a Case, J. Clin. Endocrinol. **1**:399-401 (May) 1941. Allan, F. N., and Scherer, L. R.: Insulin Resistance Due to Allergy, Am. J. M. Sc. **185**:815-821 (June) 1933. Marble, A.; Fernald, A. T., and Smith, R. M.: Effect of Human Diabetic Plasma upon Blood Sugar Curves in Rabbits Following Insulin, Endocrinology **26**:735-742 (May) 1940. Lerman, J.: Insulin Resistance—the Role of Immunity in Its Production, Am. J. M. Sc. **207**:354-360 (March) 1944. Wayburn, E., and Beckh, W.: Insulin Resistance in Diabetes Mellitus, J. Clin. Endocrinol. **2**:511-518 (Aug.) 1942. Glen, A., and Eaton, J. C.: Insulin Antagonism, Quart., J. Med. **7**:271-288 (April) 1938.

such qualitative alteration of insulin secreted by the islets of Langerhans, since the latter are frequently histologically normal at autopsy.

Recent observations support the belief that no such thing as complete insulin resistance exists, that is to say, the state of resistance to insulin can invariably be overwhelmed if enough of the hormone is administered. Two striking examples of this are the case reports of Smelo [7a] and of Boulin and his co-workers.[9] The former administered a total of 5,000 units of insulin in twenty-four hours to a female patient aged 22 years and succeeded in evoking a satisfactory hypoglycemic response. The latter workers administered 19,100 units of insulin intravenously over a period of sixteen hours, thereby rescuing a patient in profound coma in whom the alkali reserve was 19 volumes per cent. It was a perfusion of insulin at the rate of nearly 1,200 units per hour. No accident occurred other than the temporary appearance of extrasystoles.

In curious contrast to insulin, the hormones of simpler chemical structure, such as thyroxin and estrin, meet little or no resistance on the part of the body. The complex protein nature of insulin may, in part, explain this difference.[10] Whatever factors are responsible, insulin resistance is not an immediate phenomenon since it develops only some time after a course of insulin therapy is under way. It apparently develops more frequently in patients with less severe diabetes. Before resistance to insulin was established, the diabetes in most of the 57 cases reported to date was well controlled with relatively small doses of insulin.

In terms of the number of actual cases reported in the literature, true insulin resistance may be considered rare. However, while only 29 cases were reported during two decades of the insulin era, 28 cases have been reported since 1941. Thus, the incidence will doubtless rise, especially among patients who are under the care of those physicians classed by Mosenthal as the "purists." [11] Of the 57 cases reported to date, only 8 have come to autopsy (excluding the present case). In 2 instances hemochromatosis was found.[12] In another there was pan-

9. Boulin, R.; Uhry, P., and Chauderlot: On a Case of Diabetic Coma with Insulin Resistance Reduced by Intravenous Administration of 19,100 Units of Insulin, Presse méd. **55**:481 (July 19) 1947.

10. Regan, J. F.; Westra, J. J., and Wilder, R. M.: Insulin Resistance, New England J. Med. **223**:745-750 (Nov. 7) 1940.

11. Mosenthal, H. O.: Management of Diabetes Mellitus: An Analysis of Present-Day Methods of Treatment, Ann. Int. Med. **29**:79-90 (July) 1948.

12. Wood, F. C., and Fitzhugh, T., Jr.: Hemochromatosis in Metal Workers: Case Report with Autopsy and Brief Review of Literature, Arch. Int. Med. **44**: 882-892 (Dec.) 1929. Pollack, H., and Long, E. R.: Thrombosis of the Hepatic Artery with Sudden Resistance to Insulin in a Diabetic Patient, Arch. Path. **13**: 530-532 (March) 1932.

creatic fibrosis with calcareous degeneration,[13] while the fourth case disclosed active pulmonary tuberculosis.[14] In the fifth report [15] hepatic cirrhosis and total lipoatrophy were the conspicuous findings. A sixth necropsy revealed no abnormalities.[10] The seventh report [16] described necrosis of the islands of Langerhans, myocardial degeneration and hypernephroma. An eighth case [1] revealed myocardial damage and lesions in the brain.

In fatal cases every attempt should be made to obtain permission for a necropsy in an effort to demonstrate pathologic phenomena which may explain insulin resistance. Far too few necropsies have been reported to draw any conclusions.

The vacillating character of insulin resistance is difficult to explain. Its onset and subsidence in any given patient are entirely unpredictable. The onset may be gradual or sudden. Insulin may later regain its previous efficacy in from two days to three years, although one diabetic patient is reported on in whom 700 to 800 units of insulin daily were still required after five and one-half years.[7a] Of especial interest is the case of a 43 year old woman with diabetes whose insulin requirement not only dropped from 500 units daily to zero but precipitated severe spontaneous hypoglycemia. A biopsy of hepatic tissue disclosed severe fatty change with a suggestion of mild portal cirrhosis.[17] This experience accentuates the necessity of close vigilance in cases in which the patient is receiving huge doses of insulin, especially when coronary disease is a concomitant finding, since hypoglycemia may in such cases induce myocardial infarction.

MANAGEMENT OF INSULIN-RESISTANT PATIENTS

When insulin resistance is encountered in any given patient, a defeatist attitude is not justified on the part of the therapeutist until painstaking search is conducted for the factors which enhance or possibly cause the phenomenon.

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13. Mason, H. H., and Sly, G. E.: Diabetes Mellitus: A Report of a Case Resistant to Insulin but Responsive to Change in Type of CHO Fed, J. A. M. A. **108**:2016-2020 (June 12) 1937.

14. Wayburn, E.: Complete Insulin Resistance in Diabetes, Am. J. M. Sc. **190**:157-164 (Aug.) 1935.

15. Lawrence, R. D.: Lipodystrophy and Hepatomegaly with Diabetes, Lipaemia, and Other Metabolic Disturbances: Case Throwing New Light on Action of Insulin, Lancet **1**:724 (May 18); 773 (May 25) 1946.

16. Dillon, E. S.; Dyer, W. W., and Fittingoff, H.: Unpublished case report; tabulated by Smelo.[7]

17. Judd, E. S.; Kepler, E. J., and Rynearson, E. H.: Spontaneous Hypoglycemia: Report of Two Cases Associated with Fatty Metamorphosis of Liver, Am. J. Surg. **24**:345-363 (May) 1934.

There are at least three forms of insulin resistance which may be considered amenable to corrective measures. First, delayed absorption of insulin may account for a temporary need for huge doses. Such a situation, of course, constitutes an entirely unpredictable form of insulin resistance and may be extremely hazardous. It was well demonstrated by Root,[18] who employed a radioactive insulin to demonstrate delayed absorption in certain patients. Corrective measures here are resolved into utilizing other routes of parenteral administration. A second form which may be eliminated is the insulin resistance induced by decrease of the phosphate reserves in the organism.[19] This phenomenon is countenanced in diabetic acidosis when urinary loss of phosphates causes a depression of the humoral concentration of P_2O_5 ions, preventing the easy synthesis of hexose phosphate. When the ratio of phosphates to urea in the urine is less than 1 to 10, administration of phosphate is urgently indicated. Thirdly, infections of any sort should be vigorously treated and eliminated before insulin resistance is ascribed to any of the more complex causes. Allergic states, when concomitant with resistance to insulin, should be managed appropriately. Especially when allergy and resistance to insulin coexist, one may be rewarded by the disappearance of both after desensitization technics.[20]

No particular departure from the usual diabetic diet seems to mitigate the state of insulin resistance, and disagreement exists as to the effect of carbohydrates on insulin requirement. It has been variously stated that a diet high in carbohydrates may raise the insulin requirement enormously,[11] may increase the efficiency of insulin[21] or may not increase the requirement of insulin.[22]

Such substances as taurine and stilbestrol,[3] copper sulfate,[23] lipocaic[24] and many others have been tried in an effort to reduce insulin requirement, but results are variable and inconclusive. Two factors

18. Root, H. F.; Irvine, J. W.; Evans, R. D.; Reiner, L., and Carpenter, T. M.: Absorption of Insulin Labeled with Radioactive Iodine in Human Diabetes, J. A. M. A. **124**:84-90 (Jan. 8) 1944.

19. Le Gag: Insulin Resistance Through Decrease of the Phosphate Reserves in the Organism, Presse méd. **55**:767 (Nov.) 1947.

20. Karr, W. G.; Scull, C. W., and Petty, O. H.: Insulin Resistance and Sensitivity, J. Lab. & Clin. Med. **18**:1203-1211 (Sept.) 1933.

21. Sprague, R. G.: Diabetes Mellitus, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1945, vol. 9, p. 1152.

22. Himsworth, H. P.: Insulin Deficiency and Insulin Inefficiency, Brit. M. J. **1**:719 (May 4) 1940.

23. Schnetz, H.: Ueber eine insulinsparende Wirkung des Kupfers, Klin. Wchnschr. **16**:664-671 (May 8) 1937.

24. Glass, W. I.; Spingarn, C. L., and Pollack, H.: Unusually High Insulin Requirements in Diabetes Mellitus, Arch. Int. Med. **70**:221-235 (Aug.) 1942.

confuse interpretation of the results: 1. There are too few cases for statistical evaluation. 2. The initiation of therapy may coincide with spontaneous subsidence of insulin resistance.

Finally, when all contributory or inciting factors have been excluded, the management of a case of insulin resistance consists in constant vigilance over the patient and the administration of enough insulin to prevent frank acidosis, glycosuria and hyperglycemia so far as is practicable. If the insulin requirement becomes economically prohibitive to the patient, adequate funds should be made available through the local or national diabetic association. Such instances are rare enough to justify this measure.

REPORT OF A CASE

A 63 year old retired man registered at the Grand Forks Clinic on April 11, 1947, complaining of precordial pain radiating to the left arm which was definitely initiated by exertion and subsided in one to two minutes in response to complete rest and intake of 1/100 grain (0.0006 Gm.) of nitroglycerin. There had been intermittent orthopnea with edema of the ankles for the past eight years. A second complaint was urinary frequency and nocturia for the past six years, with no attacks of acute urinary retention but some delay in initiating micturition. A third complaint was epigastric distress, intermittent in character, during the past ten years which presented clinical features of the syndrome of peptic ulcer.

Inquiry into the patient's past history revealed that he had diabetes mellitus, known since 1941, and since that date he had been taking a daily dose of 10 units of protamine zinc insulin. Except for considerable fatigue and intermittent polydipsia and polyuria there had apparently been no serious symptoms incident to his diabetes. The patient stated that he had suffered two "strokes," the first occurring in 1937 and the second in 1943. The first attack apparently cleared up without leaving any residual effects, but the second attack left a residual, mild, partial hemiplegia involving the right leg and arm, with ptosis and hemifacial paralysis. In January 1946 he had a sudden attack of precordial pain which awakened him during the night and after which he was given bed rest for three months. The diagnosis of acute coronary occlusion was made elsewhere at that time. The patient stated that he used neither tobacco nor alcohol and that his only activity consisted of a few walks during the day. There was no history of allergy.

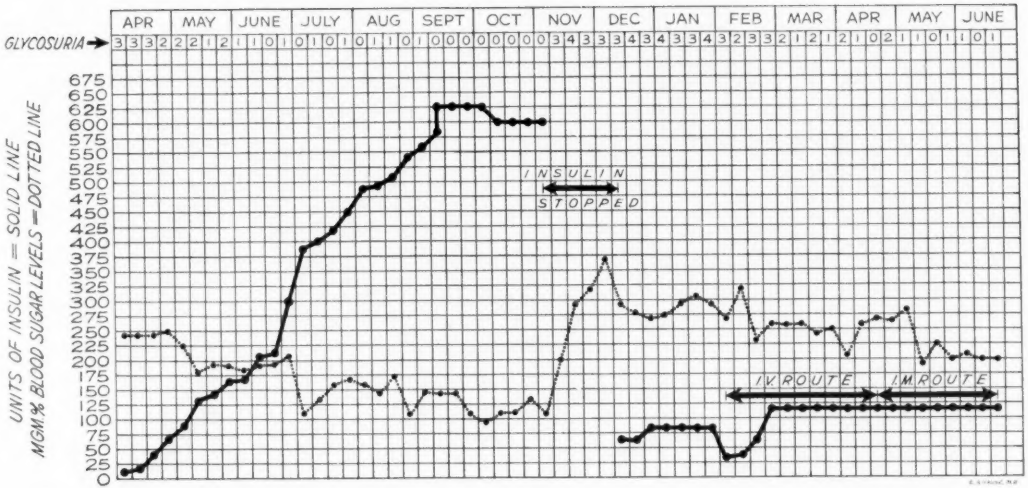
The patient was 68 inches (173 cm.) in height and weighed 176 pounds (79.8 Kg.). The blood pressure was 145 systolic and 80 diastolic. Examination of the eyes revealed a mature cataract on the right, with ptosis and right hemifacial weakness, grade II (on the basis of IV). The pupils reacted to light and in accommodation. The fundus could be observed only on the left and was normal. The mouth was edentulous. Examination of the heart revealed poor tones and a typical irregularity of auricular fibrillation. No bruit was heard. There was no enlargement on percussion. The lungs were normal except for bilateral basilar rales. The abdomen was obese, but the edge of the liver could be felt descending 4 cm. below the right costal margin on deep inspiration. The spleen was normal, and no other masses were palpable. Rectal examination revealed no abnormalities except for moderate prostatic enlarge-

ment of a benign nature. Peripheral vessels were moderately thickened and tortuous, and the dorsalis pedis and posterior tibial pulsations were feeble. Neurologic examination disclosed findings consistent with mild residual hemiplegia of the right side. Urinalysis showed sugar (4 plus) with a trace of acetone, but no diacetic acid was present. The test for albumin revealed none, and the sediment was normal. The concentration of hemoglobin and the red and white blood cell counts were normal. The sedimentation rate was 51 mm. at the end of one hour. The fasting blood sugar was 235 mg. per hundred cubic centimeters. Serologic tests for syphilis gave negative reactions. The electrocardiogram showed auricular fibrillation, a ventricular rate of 100 per minute, a depressed S-T segment in lead I and inverted T waves in leads I and II. There was slight elevation of the S-T segment in lead III. The interpretation of this was myocardial damage with auricular fibrillation. Two determinations of the blood cholesterol were carried out seven days apart, and the contents were 238 and 236 mg. per hundred cubic centimeters respectively. The results of sulfobromophthalein and cephalin flocculation tests were within normal limits. On April 14, 1947, roentgenologic and fluoroscopic examination of the gastrointestinal tract was carried out. The lungs and heart shadow were within normal limits. The esophagus, stomach and duodenum were well visualized and appeared normal except for a constantly dilated esophageal antrum.

The clinical diagnosis was as follows: (1) diabetes mellitus, grade III, (2) moderately severe generalized arteriosclerosis, including severe arteriosclerotic heart disease with anginal syndrome and auricular fibrillation, (3) residual hemiplegia involving the right side and (4) benign prostatic hypertrophy.

The patient was placed on a diet consisting of 310 Gm. of carbohydrate, 90 Gm. of protein and 100 Gm. of fat. The dosage of protamine zinc insulin was increased by 2 units daily until the fifth day after admission to the Clinic, when generalized bilaterally symmetric urticaria developed suddenly at 3 o'clock in the afternoon. This was relieved considerably by hypodermic injection of 3 minims (0.18 cc.) of epinephrine. The following morning the patient's fasting blood sugar was 235 mg. per hundred cubic centimeters and a 3 plus reaction for sugar was found in the urine, with no acetone. The use of protamine zinc insulin was discontinued because of the severe allergy which had developed, and regular insulin was given twice daily, 10 units in the morning and 10 units before supper. Thereafter the amount of regular insulin was increased regularly but gradually until it was reasonably certain that this was a case of insulin resistance (figure). The urine was tested four times a day for sugar and acetone, and determinations of blood sugar were made twice weekly or oftener throughout the entire period of observation of the patient.

During the interval from April 17 to June 9, 1947, the patient's total daily insulin dosage was increased from 10 units of protamine zinc insulin to 200 units of regular insulin, and despite this large dosage the blood sugar was found to be 190 mg. per hundred cubic centimeters on June 14, 1947. The patient had experienced no symptoms to suggest an insulin reaction at any time. Previously he had complained of fatigue and lassitude, but with increasing amounts of insulin he constantly remarked that he seemed to feel progressively more alert and energetic. At this time he was completely reexamined, and there were no new findings. With the realization of the hazard of hygoglycemic reactions in any case of coronary insufficiency, it was decided that constant vigilance would be necessary if further increase in the dosage of insulin were to be ventured. Since the patient lived but a short distance from the clinic, he was asked to come



The response of hyperglycemia and glycosuria in a case of insulin resistance in a male patient aged 63. Each month has been divided into four units of time, and each unit represents the average of glycosuria and blood sugar levels during a one week interval. The entire period of observation in this case was nearly fifteen months.

in twice daily, in the morning and in the afternoon, each time being seen and given the insulin by me. Despite a total daily dose of 300 units of insulin, which had been reached by June 28, 1947, the fasting blood sugar was 210 mg. per hundred cubic centimeters. However, the glycosuria was gradually disappearing, and by Sept. 11, 1947, the patient was completely aglycosuric and blood sugar levels were approaching the normal range in response to 620 units of insulin daily. The patient continued to be aglycosuric during the month of October, and the blood sugar remained at normal levels on a daily dose of 600 units of insulin. At no time did he give any suggestion of an insulin reaction. On Nov. 3, 1947, all insulin therapy was stopped and the patient was placed on a new diet of 150 Gm. of carbohydrate, 90 Gm. of protein and 160 Gm. of fat in an effort to lower his requirement of insulin. The rapid rise of the fasting blood sugar level to a peak of 360 mg. per hundred cubic centimeters is well illustrated in the figure. Urinalyses four times daily showed a 3 to 4 plus reaction for sugar but no acetone at any time. The patient noted a recurrence of fatigue and lassitude. One week after insulin therapy was discontinued a sample of blood was withdrawn and the serum fraction was tested for insulin-neutralizing antibodies by Dr. Francis Lowell. The results of this test were negative, the reason for which will be discussed later. Two determinations of blood cholesterol were carried out two weeks apart, while the patient was on the relatively high fat diet, and the contents were 226 and 232 mg. per hundred cubic centimeters respectively.

From Nov. 12, 1947, to Jan. 28, 1948, the patient was given 5 mg. of copper sulfate after each meal and at bed time, or four times daily. This apparently was without effect on blood sugar levels and insulin requirement (figure). He took 50 mg. of nicotinic acid four times daily from July 6 to August 30, and this also had no apparent effect on blood sugar levels, although it was actually given for head noises. Because of the poor control of glycosuria and persistently high fasting blood sugar levels, a relatively small total dose of 60 units of regular insulin was started on Dec. 9, 1947, in combination with the high fat diet. In the figure it will be seen that control of the blood sugar and the glycosuria was unsatisfactory. The insulin was increased to 40 units twice daily, still without effect. On Feb. 4, 1948, it was decided to resort to the intravenous route of insulin administration, beginning with a dose of only 14 units twice daily. This was gradually increased to a maximum of 40 units three times daily, or a total of 120 units. As illustrated, this method of treatment had only minimal effects in further depressing the hyperglycemia. However, an average of five blood sugar levels taken one hour after the intravenous administration of 40 units of regular insulin showed a significant depression of the blood sugar to 162 mg. per hundred cubic centimeters. The average of blood sugar levels taken on five different occasions, one-half hour after the intravenous administration of insulin, was 231 mg. per hundred cubic centimeters, while the average of five determinations three hours after the same intravenous doses was 195 mg. This suggests somewhat more effective control of the blood sugar levels by the intravenous route as compared with that evidenced in several determinations carried out at different times of the day while the patient was receiving a total subcutaneous dose of 200 units daily, which failed to show any significant depression of the blood sugar at any time.

On April 17, 1948, the intravenous route of administration was discontinued because of inaccessibility of veins, and intramuscular injections were started with the same total dosage. Interestingly enough, it will be observed in the

figure that even better control was apparently achieved by this route than by the intravenous route, notwithstanding the transient depressions of the blood sugar level incident to the intravenous route of injection, which are not illustrated on the graph. Thereafter, the patient received the usual dose of 40 units three times daily intramuscularly, with good control of his glycosuria but inadequate control of hyperglycemia. He was constantly interviewed for evaluation of his subjective status. There was no doubt in his mind that he felt best when on the high doses of insulin, but it was thought neither practicable nor safe to allow him to receive large doses of insulin,[25] self administered, without the constant daily vigilance of the physician. Therefore, a daily dose of 120 units was set arbitrarily as the "middle of the road"[11] approach to this problem. On June 17, 1947, he was seen at the clinic and had no complaints. The fasting blood sugar was 195 mg. per hundred cubic centimeters.

However, at 3 a. m. the following day he awoke suddenly with an acute attack of extreme dyspnea, severe precordial pain and a sudden desire to void and defecate. There was rapid development of deep cyanosis, and death occurred in fifteen minutes. I arrived a few moments after the death of the patient, and therefore this description had to be obtained from the patient's wife, who also stated that none of the symptoms of an insulin reaction (for which she had been taught to be on the alert) was in evidence, such as trembling, sweating, blurring of vision, hunger or confusion. The patient's wife had given him a half glass of orange juice at the onset of his attack, which she had been taught to do in case of any acute attack.

Necropsy revealed pulmonary edema without evidence of embolism or infarction. The heart was normal in size, but the coronary arteries were markedly sclerosed with calcification and their lumens greatly narrowed. The left anterior descending branch was almost completely obliterated in one area, and scarring of the myocardium suggested an ancient infarct. Microscopically, there was moderate diffuse fibrosis of the myocardium. The liver was normal in size and appearance, but microscopic examination revealed rather pronounced fatty degeneration. The kidneys, though grossly normal, exhibited early intercapillary glomerular sclerosis. Unfortunately, the pancreas was partially destroyed by autolysis, but enough vestiges remained to detect notable replacement fibrosis of the ducts, acini and islet tissue. The islands of Langerhans are known to be the most resistant to fibrous replacement.[26] There was no hemochromatosis, and the organ was grossly normal. The remaining organs were entirely normal.

The cause of death was presumed to be acute myocardial failure.

COMMENT

In retrospect, the reader may logically argue that daily doses in excess of 400 units of insulin were hardly mandatory in this case, except to accomplish the purist objective of complete aglycosuria and normoglycemia, which was obtained by the use of 600 or more units

25. Dr. Franklin B. Peck, of Eli Lilly and Company, furnished generous quantities of insulin for use in this investigation.

26. Barron, M.: Relation of Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis, Surg., Gynec. & Obst. **31**:437-488 (Nov.) 1920. Haunz, E. A.: Carcinoma in the Head of the Pancreas: The Effects of Obstruction upon the Ductal and Acinar Systems, Thesis, University of Minnesota (Mayo Foundation), 1946.

of insulin daily. Further, a coexisting anginal syndrome predisposes the patient to acute coronary occlusion, particularly in the event of severe hypoglycemic shock,[27] which has been known to result from an unpredictable precipitous decline in insulin requirement. Of this I was keenly aware. The so-called free dieters [11] would in all probability have managed such a patient on token doses of insulin, ignoring the hyperglycemia and glycosuria in the absence of ketosis; however, they should be reminded of the many sound objections to prolonged hyperglycemia, especially with persistent glycosuria.

The following reasons are offered in justification of investigating the insulin tolerance of the patient herein reported on: 1. There had been severe persistent hyperglycemia and glycosuria for some time, with polydipsia, polyuria and fatigue. 2. The patient felt increasingly better on increasingly higher doses of insulin. 3. He had never experienced an insulin reaction. It was believed that, in the probable absence of ketosis, infection, hepatic disease (clinically), tissue enzyme or storage depot dysfunction or immunologic inactivation, this patient might have the so-called idiopathic type of insulin resistance. However, the fatty degeneration of the liver found at necropsy may have been the basic cause of insulin resistance, but it cannot be proved. At least it is certain that neutralizing antibodies were absent, and this finding is consistent with Lowell's [28] opinion that, in general, only extremely resistant patients requiring more than 1,000 units daily give positive reactions.

In the present case it was impossible to determine just when the resistance to insulin developed, because the patient had never taken more than 10 units of protamine zinc insulin daily previous to his admission to the clinic and was entirely ignorant of his severe, persistent glycosuria, since he rarely tested his urine. However, it is of interest that insulin resistance in this patient and in the patient of Martin and others [1] was demonstrated after a generalized urticarial reaction to protamine zinc insulin. However, the latter patient died in acidosis, while the former never exhibited frank acidosis. The effect of a given dose of insulin decreases as acidosis increases.[29]

The fact that the intramuscular route of administration of insulin appeared to be more effective than either the intravenous or the subcutaneous route is probably not due to the mechanism of insulin resistance, since the intramuscular route more effectively depresses blood sugar in tests for insulin sensitivity.[30]

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27. Joslin, E. P.; Root, H. F.; White, P.; Marble, A., and Bailey, C. C.: The Treatment of Diabetes Mellitus, ed. 8, Philadelphia, Lea & Febiger, 1946, p. 514.

28. Lowell, F. C.: Personal communication to the author.

29. Rivet, L.: Insulin Resistance, Presse méd. **55**:365 (May 31) 1947.

30. Lawrence, R. D.: Hypoglycemic States, Brit. M. J. **2**:1000-1001 (Dec. 20) 1947.

At least one factor may be significant in the present case report. It illustrates the distinct possibility that a considerable number of insulin-resistant patients escape detection because rather severe hyperglycemia and glycosuria are all too often sanctioned by the "free dieters," by disinterested practitioners or by patients uneducated in their own diabetic management.

The maximum daily dose of insulin attained in this case report was 620 units. In a review of the 57 cases reported to date it was found that 15 patients received lower maximum daily doses. The point I wish to make is that the future study of insulin-resistant cases should not become merely a contest or a report of cases in which record maximum daily dosage was employed, as this would eliminate the recognition of many important cases which may serve to unravel some of the complexities of this phenomenon.

SUMMARY

1. A brief review of present day concepts of insulin resistance has been presented together with suggested principles of management of insulin-resistant patients.

2. A case is presented which required a maximum of 620 units of insulin daily to maintain normal blood sugar levels and aglycosuria. At no time were clinical signs of hypoglycemia in evidence. Death occurred seven months after the insulin dosage was reduced to 120 units daily. Necropsy revealed pronounced fatty changes in the liver and considerable coronary sclerosis with myocardial scarring. Death was believed to be due to acute myocardial failure. A definite cause of the insulin resistance could not be determined.

3. The increasing number of case reports in the literature and the nature of the present case report strongly suggest that the incidence of insulin-resistant diabetic patients is much higher than was previously supposed. Future reports are encouraged in the hope of determining the cause and cure, especially in view of the threatening worldwide shortage of insulin.

ACUTE RENAL INSUFFICIENCY

A Comparison of the Use of an Artificial Kidney, Peritoneal Lavage and More Conservative Measures in Its Management

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AND
ARTHUR GROLLMAN, Ph.D., M.D.
DALLAS, TEXAS

THE OCCURRENCE of acute oliguria or anuria as a complication of incompatible blood transfusions, after prolonged arterial hypotension or following intoxication with sulfanilamide derivatives, mercuric chloride and other compounds and the recognition that the resultant renal insufficiency may be temporary has stimulated interest in the use of an artificial kidney or peritoneal lavage in the treatment of such a condition. The reports in the current scientific literature, as well as in the lay press, describing the use of these measures give an erroneous impression of their wide field of usefulness as well as of the success attributed to their application. Our investigations on the use of the artificial kidney during the past year have demonstrated many inherent dangers which previous investigators have failed to note. We have also treated successfully patients in acute renal failure by the simpler and safer procedures to be discussed later.

REVIEW OF THE LITERATURE

The artificial kidney has been used by Kolff,[1] Alwall,[2] Murray,[3] Lam and Ponka [4] and Skeggs and Leonards.[5] In addition, reports in the

This work was supported by a grant from the Life Insurance Medical Research Fund.

From the departments of pathology and experimental medicine, the Southwestern Medical College and the Medical Services of Baylor and Parkland Hospitals.

1. Kolff, W. J., and Van Noordwijk, J.: The Artificial Kidney, Kampen, Holland, J. H. Kok, N. V., 1946.

2. Alwall, N.: On the Artificial Kidney: I. Apparatus for Dialysis of the Blood in Vitro, Acta med. Scandinav. **128**:313-325, 1947.

3. Murray, G.; Delorme, E., and Thomas, N.: Artificial Kidney, J. A. M. A. **137**:1596-1599 (Aug. 28) 1948.

4. Lam, C. R., and Ponka, J. L.: Experiences with the Murray Artificial Kidney, J. Lab. & Clin. Med. **32**:1434-1435 (Nov.) 1947.

5. Skeggs, L. T., Jr., and Leonards, J. R.: Studies on an Artificial Kidney: I. Preliminary Results with a New Type of Continuous Dialyzer, Science **108**: 212-213 (Aug. 27) 1948.

lay press indicate that it is in use in many other laboratories. The data recorded by the authors cited indicate that appreciable amounts of urea may be removed from the body by dialysis, which is readily understandable considering the rapid diffusibility of urea through semipermeable membranes. However, the authors have failed to give evidence that such dialysis has actually prolonged life in either experimental animals or patients or that the procedure has not actually been harmful despite the removal of urea. As indicated later, our own experiments have demonstrated that the application of the artificial kidney as at present recommended is liable to serious defects which may actually shorten the survival time of the uremic animal or patient.

The fact that application of the artificial kidney may have failed to prolong life has not been recognized by previous investigators except Skeggs and Leonards,[5] who stated that they "have not yet been successful in keeping the animals alive for a significantly longer period than the controls." These authors give no data on the actual survival period of their animals so that it cannot be stated that this period was shortened. The recent paper of Murray, Delorme and Thomas [3] in the ARCHIVES gives no data on animals, and the paper [6] from which it is in part reproduced fails to give any data on the survival of the animals used. In the original experiments of Kolff [1] no mention is made of any work on animals. The papers of Alwall and others [7] give data on 1 dog and 2 rabbits in which the blood urea level was lowered. The survival period of the dog was less than is usually observed in untreated controls. One of the rabbits died after five and three-quarter days from hemorrhage into the abdominal cavity, while the other survived for only seven and a half days.

Critical analysis of the data obtained on human patients also fails to indicate that any benefit was derived from its use. Thus, of the 3 patients reported on by Murray and others,[3] the patient in case 2 did not regain consciousness after application of the artificial kidney. The patients in cases 1 and 3 were apparently suffering from acute renal insufficiency of the so-called lower nephron nephrosis type in which, as shown later, spontaneous urine flow in cases of recovery usually sets in on the seventh to tenth day. There is thus no proof that the use of the artificial kidney aided these patients' recovery. The curve (fig. 7) of Murray and others [3] obtained on case 3 is entirely

6. Murray, G.; Delorme, E., and Newell, T.: Development of an Artificial Kidney: Experimental and Clinical Experiences, Arch. Surg. **55**:505-522 (Nov.) 1947.

7. Alwall, N., and Norviit, L.: On the Artificial Kidney: II. The Effectivity of the Apparatus, Acta med. Scandinav., 1947, supp. 196, pp. 250-258. Alwall, N.; Norviit, L., and Steins, A. M.: Clinical Extracorporeal Dialysis of Blood with Artificial Kidney, Lancet **1**:60-62 (Jan. 10) 1948.

comparable to that in figure 2 of Muirhead and Fromm,[8] who treated with success a patient suffering from a similar disorder without resort to either an artificial kidney or peritoneal lavage.

Of the first 15 patients treated by Kolff [1] with his artificial kidney, only 1 survived, and as indicated by Kolff,[9] "he would perhaps have survived without the aid of the 'artificial kidney,' so that the only thing this observation can prove is that it is possible to be alive after dialysis." In Kolff's second series [9] 6 patients survived among 16; however, as shown later, recovery in similar cases may occur spontaneously under more conservative management. The two patients treated by Lam and Ponka [4] with an artificial kidney similar to that used by Murray and others [3] succumbed within twelve and eight hours, respectively, so that their results likewise cannot be offered as evidence for its safety or value.

LABORATORY EXPERIMENTS

Our earliest experiments were carried out on bilaterally nephrectomized dogs to determine if the apparatus could prolong the life of such animals. Utilizing the original apparatus as described by Kolff [1] and the exact technic which he employed, we not only were unable to prolong the life of nephrectomized dogs but actually shortened the period of their survival as compared to untreated controls. Even normal animals with intact kidneys suffered deleterious effects when subjected to the artificial kidney for periods of two to three hours. This experience, we believe, explains the apparently poor results obtained by previous users of the artificial kidney and led to our further investigation of its defects and methods for their avoidance. The inherent defects in the Kolff procedure were found to be (1) the mechanical trauma induced by the pump used to return blood to the animal, (2) the uncertainty of the dosage of heparin used as anticoagulant, (3) the massive hemolysis produced by the membrane as well as by the dialyzing fluid, (4) the failure of the dialyzing solution to control adequately the water and electrolyte balance and (5) variations in the blood content of the apparatus which resulted in depletion or overload of the vascular system.

The aforementioned difficulties have been eliminated or reduced to a minimum to the extent that we have been able to prolong successfully the life of nephrectomized dogs up to nineteen and a half days and that of dogs with renal excretory function eliminated by other means up to the thirtieth day.

To illustrate the fallacy of trying to evaluate the efficacy of any artificial kidney in terms of removal of urea or nonprotein nitrogen alone, the survival of 8 nephrectomized dogs treated by the technic of Kolff is presented in the accompanying table. From 4.7 to 29.5 Gm. of urea was removed from these animals in from 0.7 to 3.0 hours of dialysis. However, it should be noted that the animals from which most urea was removed had the shortest survival periods. Analysis of the plasma (sodium, chloride and carbon dioxide-combining power) in these experiments showed that although the animal was theoretically improving as regards removal of

8. Muirhead, E. E., and Fromm, C. S.: Severe Acute Renal Insufficiency with Recovery, J. A. M. A. **137**:1378-1382 (Aug. 14) 1948.

9. Kolff, J.: The Artificial Kidney, J. Mt. Sinai Hosp. **14**:71-79 (July-Aug.) 1947.

waste products, the chemical composition of its body fluids were concomitantly being severely altered. Thus the removal of urea, which most authors have used for evidence of improvement of the patient, is not a sufficient criterion to evaluate the effect of an artificial kidney. This fact was further proved by experiments in which 9 normal dogs were subjected to treatment with the artificial kidney for 0.5 to 2.0 hours. They all died within three days, during which period there was marked hemoglobinuria as a result of the hemolysis produced by the procedure.

CLINICAL RESULTS

It has been intimated by advocates of the use of peritoneal irrigation and the artificial kidney that the application of such measures has averted a fatal outcome. In support of this contention, the claims are made that (1) the patient was in a grave condition or rapidly deteriorating and (2) survival for any period is significant since the mortality rate

Survival of Bilaterally Nephrectomized Dogs Following Application of the Artificial Kidney *

Initial Plasma Urea Level, Mg./100 Cc.	Final Plasma Urea Level, Mg./100 Cc.	Urea Removed, Gm.	Survival, Hours
316	261	4.7	27
197	134	5.2	18
335	244	6.7	1
380	232	10.5	4
335	162	14.4	15
405	265	14.7	9
535	304	16.1	6
458	176	29.5	3.3

* Despite the removal of urea, survival time was actually reduced in comparison with that observed in control animals not subjected to the procedure.

from acute renal insufficiency is so high. However, a study of 27 patients observed by us during the past two years has demonstrated that their clinical well-being during eight to twelve days of anuria and oliguria depends greatly on the management of their electrolyte and water balance during this period.

Patients with oliguria are easily overloaded with water or salt and suffer mental deterioration and cerebral manifestations with or without the onset of generalized edema. Such manifestations have frequently been ascribed to "uremia," as in the case reported by Muirhead, Small and McBride,[10] whose patient appeared to be in a terminal state with generalized edema, mental deterioration and muscular irritability. Peritoneal irrigation with a solution of crystalloids aggravated

10. Muirhead, E. E.; Small, A. B., and McBride, R. B.: Peritoneal Irrigation for Uremia Following Incompatible Blood Transfusion, Arch. Surg. **54**:374-381 (April) 1947.

these symptoms despite the removal of urea from the body. However, irrigation of the peritoneum with 5 per cent glucose in distilled water initiated the removal of substantial quantities of salt from the body, diuresis and ultimate recovery. In this patient the so-called uremic symptoms disappeared when an overload of salt was corrected by peritoneal lavage. In the light of our present knowledge, the peritoneal irrigation was beneficial insofar as it corrected an abnormality that was induced by a previous overload with isotonic sodium chloride solution.

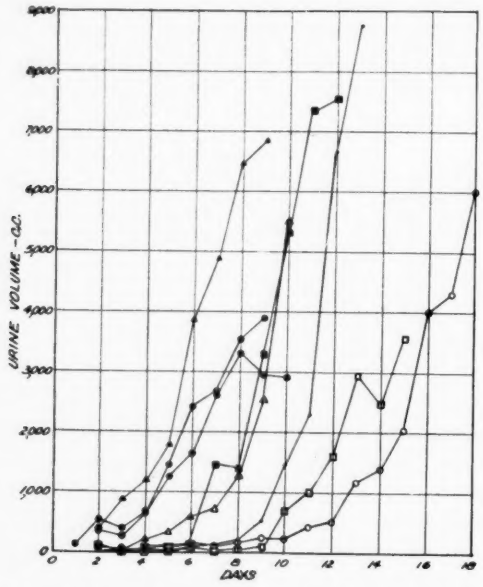

Fig. 1.—Curves for urinary output of 8 patients with acute renal insufficiency following incompatible blood transfusions. Note that periods of two to ten days of oliguria are followed by periods of spontaneous diuresis. Recovery occurred in all these patients without resort to the use of an artificial kidney or peritoneal lavage.

There is a general tendency in the presence of anuria or oliguria to infuse large quantities of fluids in an attempt to initiate diuresis and eliminate accumulating waste products from the body. However, the changes in the kidneys in acute renal failure are such as to render the desired response impossible. The only effect of such a procedure is to cause an overload of salt water and the appearance of symptoms

erroneously attributed to uremia. Thus, Frank, Seligman and Fine [11] reported the following in regard to their patient:

> During the first four hospital days the daily urine output was 30 cc., 200 cc., 0 cc. and 0 cc. respectively. Oral fluid was supplemented with intravenous 5 per cent glucose in water until the daily intake ranged from 5 to 7 liters per day. Increased ascites and generalized edema developed. . . . On the fifth hospital day the patient's condition was critical.

The patient of Reid, Penfield and Jones,[12] with a negligible urinary output for ten days, was given about 24,500 cc. of fluid. Edema became prominent. Goodyear and Beard [13] stated that "infusion of isotonic solution of three chlorides and alkalinization with sodium bicarbonate given intravenously failed to promote the excretion of urine. Within three days the patient's condition had become critical." The third

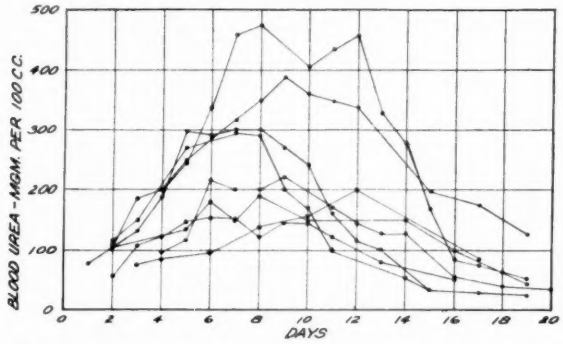

Fig. 2.—The blood urea levels of the 8 patients represented in figure 1. The urea level in each case was inversely proportional to the urinary output.

patient of Murray, Delorme and Thomas [8] received about 27 liters of fluid during the first eight day period, when the urinary output was negligible. It was observed that "the patient was showing signs of uremia."

It is apparent that in these cases, in which artificial measures were used, the grave condition of the patients and the "uremic" manifestations

11. Frank, H. A.; Seligman, A. M., and Fine, J.: Treatment of Uremia After Acute Renal Failure by Peritoneal Irrigation, J. A. M. A. **130**:703-705 (March 16) 1946.

12. Reid, R.; Penfield, J. B., and Jones, R. N.: Anuria Treated by Renal Decapsulation and Peritoneal Dialysis, Lancet **2**:749-753 (Nov. 23) 1946.

13. Goodyear, W. E., and Beard, D. E.: The Successful Treatment of Acute Renal Failure by Peritoneal Irrigation, J. A. M. A. **133**:1208-1210 (April 19) 1947.

were induced by the fluid overload. If this is avoided, no such symptoms appear. Thus in a recent patient observed by us the total urinary output for eight days following sulfathiazole intoxication was only 40 cc. However, the patient remained mentally alert and free of "uremic" symptoms. Similar observations have been made in our other patients

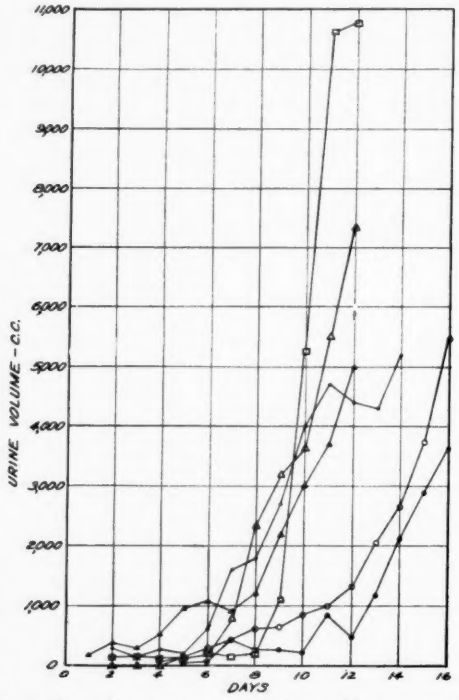

Fig. 3.—Curves for urinary output of 6 patients with acute renal insufficiency treated by the conservative measures outlined in this paper. Squares, small black circles and white circles indicate patients with acute hemolysis due to absorption of water from irrigation following prostatectomy, black and white triangles patients with peripheral vascular shock following hemorrhage and large black circles a patient with acute carbon tetrachloride poisoning.

in whom overload with salt and water was avoided and in experimental animals maintained after nephrectomy on an electrolyte-free diet.[14]

It is generally stated that the mortality rate among patients with acute renal insufficiency is 80 to 90 per cent. Our experience with

14. Grollman, A.; Muirhead, E. E., and Vannatta, J.: Am. J. Physiol., to be published.

27 consecutive cases of severe acute renal failure due to various causes contradicts this, as demonstrated by 4 fatalities, or a mortality rate of only 15 per cent. In the 4 patients who died, the diuresis had attained a peak, and, therefore, they demonstrated adequate renal recovery. Autopsies revealed the following causes of death: (1) punctate cerebral hemorrhages and cortical degeneration; (2) pulmonary embolism and cerebral hemorrhages; (3) postoperative pelvic hemorrhage, and (4) bronchopneumonia and pulmonary embolism. Death of these patients occurred on the thirteenth, ninth, ninth and twenty-eighth day, respectively, after the onset of the renal failure. Figure 1 reproduces the data on 8 patients, all of whom recovered despite an oliguria bordering on anuria which extended from two to ten days. Obviously the use of an artificial kidney or peritoneal lavage in these patients was unnecessary. All the patients referred to in figure 1 had a considerable degree

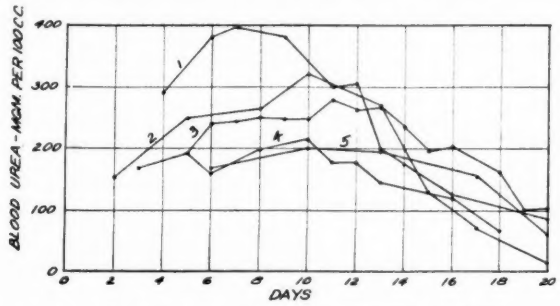

Fig. 4.—The blood urea levels of patients represented in figure 3. Curve 1 is that of a patient with peripheral vascular shock following hemorrhage; curves 2, 3 and 4 are those of patients with acute hemolysis following irrigation with water after prostatectomy, and curve 5 is that of a patient with acute carbon tetrachloride poisoning.

of uremia, as shown in figure 2, despite which recovery occurred. The patients of figures 1 and 2 had acute renal insufficiency induced by transfusion of incompatible blood. That a similar state of affairs exists in cases of oliguria from other causes is shown in figure 3, in which data are presented on patients suffering from acute hemolysis, shock and carbon tetrachloride poisoning. The course of the urinary output as shown in figures 1 and 3 follows a characteristic curve, with a period of anuria or oliguria followed by diuresis. The urinary output increases slowly at first but later rapidly enters into the diuretic phase. The entire process follows a characteristic course. The peak of the diuresis may occur on the eighth to eighteenth day, depending on the severity of the case. As the diuresis progresses, the loss of fluid must be replaced by salt and water, the blood urea level drops toward normal and

recovery begins. Of interest is the demonstration that the use of artificial measures so far recorded in the literature has not altered this characteristic mode of recovery. Thus in cases in which artificial measures are used a similar series of changes in the urinary output occurs. Recovery, therefore, seems to require a certain interval whether artificial measures are used or not.

In figure 5 are reproduced the curves for urinary output of the 3 patients cited in the literature in whom an artificial kidney has been used. Comparison of these curves with those of figures 1 and 3 illustrate that the results cited from the literature do not constitute proof of the need for the use of this artificial procedure. The same may be said for the results obtained by peritoneal lavage shown in figure 6.

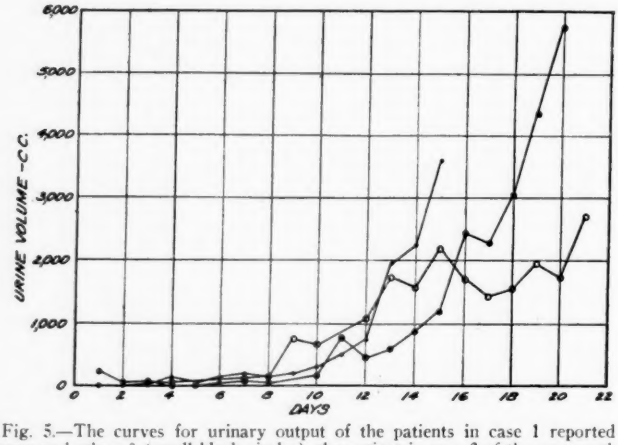

Fig. 5.—The curves for urinary output of the patients in case 1 reported by Murray and others [3] (small black circles), the patient in case 3 of the same authors (white circles) and the patient in case 17 of Kolff [1] (large black circles), who survived the application of the artificial kidney. Note the delayed diuretic response as compared to that in patients represented in figures 1 and 3 who were treated conservatively.

It is argued that artificial measures lengthen the period of survival, thus allowing time for renal recovery. Figures 1 through 6 demonstrate that ordinarily a sufficient backlog of waste products does not accrue even in severe cases of acute renal insufficiency, if properly managed, during the required eight to ten day period to be fatal. Indeed, the record so far for peritoneal irrigation or the artificial kidney tends to indicate that harm rather than good has resulted from their application. The use of peritoneal irrigation has been frequently associated with an augmentation of the overload of water and salt. The number of patients not surviving the application of the artificial kidney is still much in excess of the few who have recovered.

Our procedure for the proper management of acute renal insufficiency consists essentially of (1) overcoming peripheral vascular shock when present by the prompt administration of whole blood or plasma; (2) administering only such amounts of water and glucose solutions as are required to prevent dehydration and no salt except in the amount lost by diarrhea, vomiting or profuse sweating, and (3) administering adequate amounts of salt and water when diuresis sets in so as to maintain a normal water and electrolyte balance. It is obviously harmful to administer salt solution or excessive amounts of water to a patient with acute renal insufficiency since this can only result in overloading of the tissues, with the symptoms noted previously.

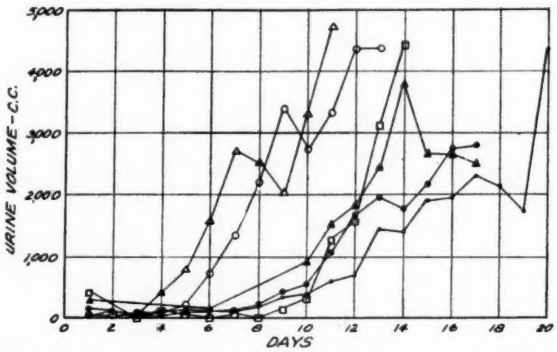

Fig. 6.—The curves for urinary output of patients with anuria following (1) mercuric chloride poisoning (Localio, S. A.; Chassin, J. L., and Hinton, J. W.: J. A. M. A. **137**:1592-1596 [Aug. 28] 1948) (white triangles); (2) sulfonamide overdosage[11] (white circles); (3) incompatible blood transfusion[12] (squares); mercuric chloride poisoning[9] (black triangles); (5) incompatible blood transfusion[13] (large black circles), and (6) incompatible blood transfusion[10] (small black circles). Note the relatively poor diuresis in these patients subjected to peritoneal lavage as compared to the patients of figures 1 and 3 and the delayed recovery phase, which is particularly evident in curves 5 and 6.

COMMENT

This critical analysis of the available data does not aim to discredit the idea that the use of an artificial kidney, peritoneal lavage or other measures for removing waste products would not be desirable for certain patients. We merely wish to emphasize that the procedure as at present available has not been proved to be safe or valuable and that many patients so treated can be more effectively and more safely handled by simpler available measures. We are at present engaged in attempting to perfect a practical and safe artificial kidney. Until a given procedure has been proved capable of consistently prolonging the

life of the nephrectomized animal, it is hazardous, in our experience, to apply it to a patient. It is preferable to rely on the normal course of events which, as we have shown, results, in most cases, in spontaneous recovery of renal function if the patients are not overloaded with salt and water in the vain attempt to stimulate urine production.

SUMMARY AND CONCLUSIONS

The application of the artificial kidney of Kolff in nephrectomized dogs failed to prolong their life despite an adequate removal of urea from the animals. Modification of the procedure led to prolongation of life of animals without renal excretory function for as long as a month.

Clinical data are presented which demonstrate that, contrary to current views, recovery may occur even after periods of anuria as long as eight days. A review of the literature indicates that patients surviving the application of the artificial kidney or peritoneal lavage would have probably survived without the application of these radical measures had their original course been managed in a rational manner. The value and necessity of these measures for such patients are questioned.

Because of the dangers inherent in the application of the artificial kidney, as at present available, or of peritoneal lavage, the use of safer procedures for the treatment of acute renal failure is advocated. The results obtained by the latter method compare favorably with those claimed for the more heroic but dangerous procedures of peritoneal lavage and the employment of the artificial kidney.

COLLOID OSMOTIC PRESSURE IN CHRONIC HEPATITIS

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AND
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DURING the course of the epidemic of acute infectious hepatitis occurring in Denmark at the time of this report, several cases of chronic hepatitis were noted in elderly women.[1] The characteristics of this form of hepatitis seem to be a grave, usually fatal, course, during which considerable changes take place in the plasma proteins: The value for serum albumin falls and that for serum globulin rises, and symptoms develop suggesting a low colloid osmotic pressure, viz., ascites and edema. The works which so far have dealt with the relation of colloid osmotic pressure to chronic hepatitis are few; moreover, the results published do not agree.[2] Myers and Keefer,[3] Tumen and Bockus [4] and Post and Patek [5] noted a decrease in plasma albumin and accordingly suggested low colloid osmotic pressure as a cause of edema; however, the pressure was not measured directly. Consequently, we thought it justifiable to take advantage of the present accumulation

From the Third Department, Kommune Hospital; Dr. Poul Iversen, Chief.
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1. Alsted, G.: Am. J. M. Sc. **213**:257, 1947. Bjørneboe, M., and Brøchner-Mortensen, K.: Ugesk. f. læger **107**:715, 1945. Bjørneboe, M.; Jersild, M.; Lundbæk, K.; Tyssing, E.; Hess, E., and Thayssen, E. H.: To be published. Jersild, M.: Ugesk. f. læger **107**:819, 1945. Jersild, M.: New England J. Med. **237**:8, 1947.

2. (*a*) Butt, H. R.; Snell, A. M., and Keys., A.: Plasma Protein in Hepatic Disease: Study of Colloid Osmotic Pressure of Blood Serum and of Ascitic Fluid in Various Diseases of Liver, Arch. Int. Med. **63**:143 (Jan.) 1939. (*b*) Kellermann, V.: Ztschr. f. d. ges. exper. Med. **100**:336, 1937. (*c*) Ralli, E. P.; Robson, J. S.; Clarke, E., and Hoagland, C. L.: J. Clin. Investigation **24**:316, 1945.

3. Myers, W. K., and Keefer, C. S.: Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of Liver, Arch. Int. Med. **55**:349 (March) 1935.

4. Tumen, H., and Bockus, H. L.: Am. J. M. Sc. **193**:788, 1937.

5. Post, A. J., and Patek, A. J. Jr.: Serum Proteins in Cirrhosis of Liver: Relation to Prognosis and to Formation of Ascites, Arch. Int. Med. **69**:67 (Jan.) 1942; Serum Proteins in Cirrhosis of Liver: Nitrogen Balance Studies on Five Patients, ibid. **69**:83 (Jan.) 1942.

of cases of chronic hepatitis to examine the problems associated with the pathogenesis of edema in this disease by measuring the colloid osmotic pressure.

The questions were:

1. Is there a sharp limit to the colloid osmotic pressure below which edema and ascites develop? If so, where does the limit lie?

2. Is there any numerical relation between colloid osmotic pressure and plasma proteins whereby the colloid osmotic pressure may be calculated when the plasma albumin and plasma globulin concentrations are known?

3. Is reduction of the colloid osmotic pressure an adequate explanation for the occurrence of ascites, or must a stasis in the portal vein, and possibly also a capillary lesion, be assumed as the cause?

In 1927, Iversen and Nakazawa[6] demonstrated the existence of a fairly sharp limit to the colloid osmotic pressure, the patients in their series with nephrogenic edema all having a pressure lower than 240 to 270 mm. of water. Butt, Snell and Keys,[2a] in 1939, reported 23 cases of subacute and chronic atrophy of the liver. They stated that most of the patients had a greatly reduced colloid osmotic pressure; they were, however, unable to observe any constant edema limit, although the lowest values were found for patients with edema and ascites.

Several workers have set up formulas for the dependence of the colloid osmotic pressure on the albumin and globulin concentrations.[7] It is a common feature of all these formulas that they express the fact that the albumin has much the greater influence on the height of the colloid osmotic pressure, owing to the smaller size of its molecules. Examples are Govaerts' formula,[7b] k (colloid osmotic pressure) $= 3.9\,A + G$, and Farkas' formula,[7a] $2.7\,A + G = k$ (colloid osmotic pressure), where A represents the value for albumin, G the value for globulin and k a constant.

On the cause of ascites in cirrhosis of the liver, most authors seem to agree, it being assumed that both the reduced colloid osmotic pressure and the portal hypertension arising as a result of the contraction of the liver play a part. This opinion was first advanced by Iversen.[8]

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6. Iversen, P., and Nakazawa, F.: Biochem. Ztschr. **191**:307, 1927.

7. (*a*) Farkas, G.: Ztschr. f. d. ges. exper. Med. **53**:666, 1927. (*b*) Govaerts, P.: Compt. rend. Soc. de biol **93**:441, 1925; **95**:724, 1926. (*c*) Wells, H. S.: Youmans, J. B., and Miller, D. G.: J. Clin. Investigation **12**:1103, 1933. (*d*) Wies, C. H., and Peters, J. P.: ibid. **16**:93, 1937.

8. Iversen, P.: Klin. Wchnschr. **7**:2001, 1928.

METHOD

For the determination of the colloid osmotic pressure, we employed Krogh's method,[9] with small collodium membranes, their permeability being tested with water and proteins. Six tests were made with each serum. The error of the method was about 10 mm. of water.

The fractionated determination of the plasma proteins was made by Henriques and Klausen's method,[10] using precipitation with ammonium sulfate. The deviation in two determinations did not exceed 0.1 per cent of the protein value.

The blood was taken without the addition of any anticlotting medium from patients in bed. The patient must be lying down, as the concentration of plasma protein rises when the patient is in the erect posture, owing to the filtering of fluid into the lower extremities.[11]

The series consisted of 31 patients with hepatitis, of whom 9 had the acute form of the disease and 22 the chronic form, in addition to 13 patients with conditions unlikely to affect the value for serum proteins, such as head injury and neuroses.

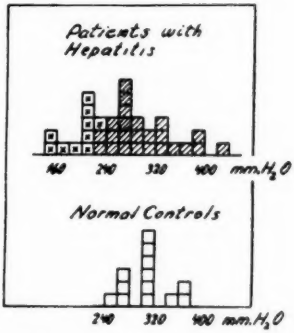

Chart 1.—Colloid osmotic pressure in patients with hepatitis and in normal controls. Squares with crosses indicate values for patients with ascites and edema, cross hatched areas, values for patients with hepatitis only, and clear areas, values for normal controls.

RESULTS OF TESTS

The data in chart 1 and in the table are arranged according to the colloid osmotic pressure. It may be seen from the chart that there was a fairly sharp edema limit at a pressure of 220 to 240 mm. of water.

The data on results of the test for colloid osmotic pressure shown in chart 2 were compiled partly in relation to the albumin concentration alone and partly in relation to the value $(3.56A+G)$. This value,

9. Krogh, A., and Nakazawa, F.: Biochem. Ztschr. **188**:247, 1927.

10. Henriques, V., and Klausen, U.: Biochem. Ztschr. **254**:414, 1932.

11. Thompson, W. O.; Thompson, P. K., and Dailey, M. E.: Proc. Nat. Acad. Sc. **14**:94, 1928.

Results of Tests on Authors' Patients

No.	Sex	Age, Yr.	Diagnosis	Edema and Ascites	Total Protein, Gm. per 100 Cc.	Serum Albumin, Gm. per 100 Cc.	Serum Globulin, Gm. per 100 Cc.	Colloid Osmotic Pressure, Mm. of Water
1	♀	44	Acute infectious hepatitis	—	6.85	4.22	2.63	321
2	♀	25	Acute infectious hepatitis	—	7.25	4.79	2.46	326
3	♀	33	Acute infectious hepatitis	—	6.76	4.57	2.19	259
4	♂	37	Acute infectious hepatitis	—	7.93	5.24	2.69	426
5	♂	34	Acute infectious hepatitis	—	6.21	3.88	2.33	276
6	♀	39	Acute infectious hepatitis	—	6.94	4.23	2.71	261
7	♀	26	Acute infectious hepatitis	—	8.04	4.74	3.30	391
8	♀	35	Acute infectious hepatitis	—	6.94	4.34	2.60	302
9	♂	55	Acute infectious hepatitis	—	7.44	3.67	3.77	273
10	♀	56	Chronic hepatitis	+	6.59	2.32	4.27	203
11	♀	55	Chronic hepatitis	+	8.10	2.12	5.98	201
12	♀	56	Chronic hepatitis	—	9.73	3.66	6.07	304
13	♀	63	Chronic hepatitis	—	7.15	3.96	3.19	327
14	♀	37	Chronic hepatitis	—	7.38	3.47	3.91	287
15	♂	55	Chronic hepatitis	—	7.95	4.87	3.08	371
16	♀	81	Chronic hepatitis	—	7.48	3.00	4.48	272
17a	♂	54	Chronic hepatitis	—	6.76	3.31	3.45	237
17b	♂	54	Chronic hepatitis	+	6.39	2.56	3.83	189
18	♀	69	Chronic hepatitis	—	6.03	3.24	2.79	256
19a	♀	64	Chronic hepatitis	—	7.27	3.72	3.55	265
19b	♀	64	Chronic hepatitis	+	6.60	2.72	3.88	160
20	♀	63	Chronic hepatitis	—	8.19	4.07	4.12	284
21	♂	65	Chronic hepatitis	+	7.71	2.60	5.11	229
22	♀	77	Chronic hepatitis	—	7.99	2.48	5.51	244
23	♀	65	Chronic hepatitis	+	7.30	1.79	5.51	219
24	♂	17	Chronic hepatitis	—	7.99	4.42	3.57	356
25	♀	51	Chronic hepatitis	—	6.99	3.41	3.28	237
26	♀	63	Chronic hepatitis	+	7.50	2.00	5.50	206
27	♀	58	Chronic hepatitis	—	8.49	3.57	4.92	299
28	♀	62	Chronic hepatitis	—	7.79	2.96	4.83	290
29	♀	53	Chronic hepatitis	—	9.43	2.62	6.81	274
30	♀	70	Chronic hepatitis	+	6.85	2.41	4.44	153
31a	♀	62	Chronic hepatitis	+	3.54	2.56	0.98	151
31b	♀	62	Chronic hepatitis	+	5.21	3.30	1.91	201
32	♂	36	Neurosis	—	7.48	4.91	2.57	375
33	♀	22	Neurosis	—	8.03	5.58	2.45	361
34	♂	39	Neurosis	—	6.65	5.04	1.61	300
34	♀	68	Neurosis	—	6.94	4.64	2.30	303
36	♂	37	Neurosis	—	7.09	4.98	2.11	275
37	♀	55	Prolapse of intervertebral disk	—	7.36	4.94	2.42	301
38	♀	57	Head injury and sequelae	—	8.23	5.71	2.52	304
39	♀	52	Head injury and sequelae	—	7.06	4.47	2.59	310
40	♀	58	Miosis	—	6.79	4.19	2.60	256
41	♀	51	Neurosis	—	6.69	4.79	1.90	277
42	♀	48	None	—	6.98	5.10	1.88	269
43	♀	49	Adiposity	—	7.15	4.61	2.54	302
44	♀	31	Neurosis	—	6.75	4.56	2.19	308

the linear relation between the colloid osmotic pressure and the concentration of serum proteins, was obtained by the method of least squares. The formula is $3.56A + G = k$ (colloid osmotic pressure); k is equal to 16. Both charts show considerable dispersion, although use of the formulas seems to give a somewhat better result. The dispersion on the determination of the colloid osmotic pressure with this formula

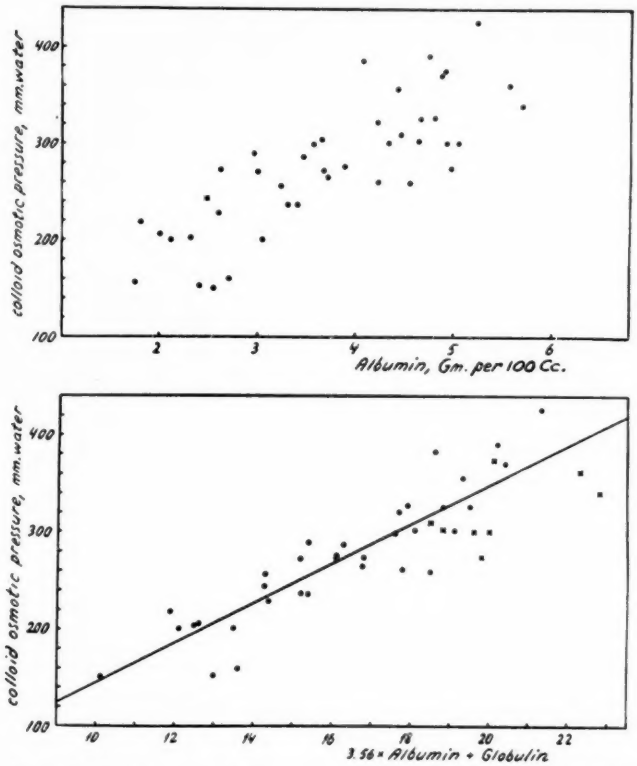

Chart. 2.—Relation of colloid osmotic pressure to albumin and globulin concentrations.

was 33 mm. of water, which must be said to be considerable; however, it was of the same dimensions as those in other investigations. It was twice the dispersion calculated from the analytic errors of the methods involved (16.5 mm. of water); the difference may have been due to analytic errors in the separation of the protein fractions or to other factors, such as the Donnan effect.

The results suggest that the reduction of the colloid osmotic pressure is the principal factor in the pathogenesis of ascites in cases of chronic hepatitis, and that portal hypertension plays a subordinate role. This view is supported by the following observations:

1. Ascites occurs only in patients whose colloid osmotic pressure is low; the limit seems definite.

2. Ascites usually develops concurrently with edema.

3. Ascites may then disappear, a fact in agreement with the theory of portal hypertension as the main cause.

4. Pronounced esophageal varices are a rare pathoanatomic observation in the form of chronic hepatitis seen in the present epidemic.

One patient with ascites and edema received blood transfusions, six (a total of 3 liters of blood) being given in six days. With this treatment the colloid osmotic pressure rose from 151 to 201 mm. of water, while the total protein concentration rose from 3.5 to 5.2 Gm., and the albumin concentration from 2.6 to 3.3 Gm., per hundred cubic centimeters; the ascites and edema persisted unchanged. This patient had already had paracenteses at intervals of a few weeks (on each occasion about 20 liters of protein-rich ascitic fluid was withdrawn); so one may take it that her protein depots were small. Apparently, what is required in such cases is the administration of still larger supplies of protein before an effect of therapy appears in the form of a rise in the colloid osmotic pressure above the limit for edema and ascites.

Chart 3 presents analyses of both serum proteins. The material for this chart was supplemented with 29 analyses of serum proteins from another study,[12] representing 7 cases of acute and 22 cases of chronic hepatitis. Accordingly, the total material consists of 13 normal persons and 60 patients with hepatitis.

The sharp edema limit in chart 3 may also be expressed by the formula. If the value for $(3.56A+G)$ is less than 14.2 for a given serum, the patient probably has ascites and edema; the chart indicates but 1 exception to the rule. This is peculiar, for we found a rather large dispersion in the determination of the colloid osmotic pressure from the formula.

The chart also indicates that the value for albumin falls as that for globulin rises, though it is difficult to draw up a definite formula for the relation between the two. The phenomenon may occur in one, or both, of the following ways:

1. High globulin values are accompanied with low albumin values because both correspond to a severe degree of morbidity. In a case of severe hepatitis a serious lesion of the liver may be expected, with

12. Bjørneboe, M.: Acta med. Scandinav. **123**:393, 1946.

a reduced output of albumin, whereas the globulin concentration will be high, owing to the vigorous formation of antibodies.

2. High globulin values are accompained with low albumin values because the organism endeavors to maintain a normal colloid osmotic pressure. In the aforementioned work [12] one of us (M. B.) advanced the hypothesis that a regulating mechanism of this sort exists whose function is to adjust the colloid osmotic pressure to normal values when the serum proteins vary.

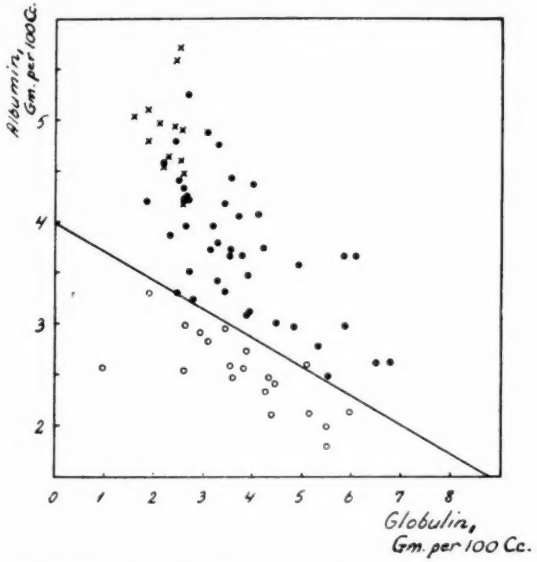

Chart. 3.—Relation between values for serum albumin and those for serum globulin. Circles indicate patients with hepatitis, ascites and edema; dots, those with hepatitis alone, and crosses, normal controls.

In chart 1 it may be seen that there is a normal (gaussian) distribution of hepatitis material so far as the colloid osmotic pressure is concerned, regardless of the occurrence of ascites and edema. This finding is in opposition to the theory that a regulating mechanism, capable of maintaining normal colloid osmotic pressure, is present in patients without ascites and edema. If there were such a mechanism, one would expect a two-peaked or an oblique curve with its peak displaced to the normal area, as the regulating mechanism would maintain the colloid osmotic pressure at normal values in a large number of cases. The average colloid osmotic pressure in patients without

ascites and edema and that in normal persons, however, were practically the same, a fact which indicates that there was no regulating mechanism in the former.

The problem cannot be solved from the present material, which must be regarded as unsuitable for such an investigation, since the production of both albumin and globulin was subjected to strong influences.

SUMMARY

Thirty-four determinations of the colloid osmotic pressure were made on 31 patients with hepatitis (9 with the acute and 22 with the chronic form of the disease) and on 13 normal subjects.

A sharp limit to colloid osmotic pressure above which edema and ascites did not appear was noted at 220 to 240 mm. of water, for which reason reduction in the colloid osmotic pressure is assumed to be the chief cause of the occurrence of ascites in this condition.

After comparison of the values for serum albumin and serum globulin with the colloid osmotic pressure, we have set up the formula $3.56A + G = k$ (colloid osmotic pressure), k being equal to 16. The dispersion of the calculated colloid osmotic pressure was 33 mm. of water. If $3.56\ (A + G) < 14.2$, a patient usually has edema and ascites.

In the analyses for serum protein it was noted that the value for albumin fell as globulin values rose. The causes of this factor are discussed.

ACTIVITY OF CARBON ANHYDRASE IN THE BLOOD

Study of Patients with Dyspnea Consequent to Chronic Cardiac and Pulmonary Disease

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AND
H. D. LEWIS, M.D.
With the Technical Assistance of
M. TAYLOR
BOSTON

THE EXTENSIVE and serious disturbances of cardiorespiratory function which result from diseases of the heart or lungs have been studied exhaustively by many investigators.[1] The consequences of these diseases include a variety of compensatory changes which mitigate to some extent the harmful or discomforting effects of the diseases themselves. Among the respiratory enzymes, hemoglobin offers an example of such a compensatory change by its increase in chronic anoxic states effected by an increase in blood volume in congestive failure and by an increase in red cell mass in severe chronic pulmonary disease. Other respiratory enzymes have not, however, been studied extensively in instances of disease. Only fragmentary observations have been made on the effect of disease on the activity in the blood of carbonic anhydrase, the enzyme which is involved in the transport of carbon dioxide. Hodgson [2] and Lambie,[3] on the basis of a small number of measurements made by means of a method of low accuracy, concluded that blood from some patients with cyanosis consequent to cardiac or respiratory disease may exhibit increased carbonic anhydrase activity. The development of a method of greater validity [4] made desirable the

From the Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

This work was done under a contract between Harvard University and the Office of Naval Research, United States Navy.

1. Altschule, M. D.: Physiology, in Diseases of the Heart and Lungs, Cambridge, Mass., Harvard University Press, to be published.

2. Hodgson, T. H.: The Carbonic Anhydrase Content of Blood in Pathological States in Man, Brit. J. Exper. Path. **17**:75, 1936.

3. Lambie, C. G.: Observations on the Carbonic Anhydrase of the Blood in Anæmia and in Other Pathological Conditions, Edinburgh M. J. **45**:373, 1938.

4. Altschule, M. D., and Lewis, H. D.: Measurement of Blood Carbonic Anhydrase Activity at Body Temperature, to be published.

reinvestigation on a more extensive scale of the effects of chronic cardiac and respiratory disease on the activity of the enzyme in the blood.

Effect of Disease on the Activity of Carbonic Anhydrase in the Blood

Case	Age	Sex	Hematocrit Value, per Cent Erythrocytes	Erythrocyte Count, Billions/Cc. Blood	Hemoglobin, Gm./Cc. Blood	Carbonic Anhydrase, Units/Cc. Blood	Carbonic Anhydrase, Units/Cc. Erythrocytes	Carbonic Anhydrase Units/Billion Erythrocytes	Carbonic Anhydrase, Units/Gm. Hemoglobin	Comment
					Chronic Cardiac Decompensation					
1	69	M	52.0	5.00	0.162	1.4	2.7	0.28	0.09	
2	68	F	43.5	3.94	0.160	1.6	3.7	0.41	0.10	
3	47	F	40.0	4.73	0.124	1.5	3.8	0.32	0.12	
4	50	M	41.0	3.90	0.141	1.3	3.2	0.33	0.09	
5	50	F	39.6	3.16	0.120	2.0	5.1	0.41	0.12	
6	37	F	54.5	6.69	0.176	1.7	3.1	0.25	0.10	Pulmonary fibrosis
7	47	F	46.0	4.21	0.138	1.7	3.7	0.40	0.12	
8	42	F	42.0	4.89	0.137	1.4	3.3	0.29	0.10	
9	46	F	53.0	5.27	0.159	1.6	3.0	0.30	0.10	
10	56	M	49.5	4.79	0.172	1.6	3.2	0.33	0.09	
11	72	M	25.5	3.14	0.077	1.3	5.1	0.41	0.17	Bleeding ulcer
12	62	M	43.0	5.44	0.140	1.5	3.5	0.28	0.11	
13	51	F	49.0	5.08	0.137	1.9	3.9	0.37	0.12	
14	48	F	31.0	3.41	0.108	1.3	4.2	0.38	0.12	Malnutrition
15	68	M	54.5	5.75	0.164	1.6	2.9	0.28	0.10	
16	60	M	40.2	5.80	0.138	1.7	4.2	0.29	0.12	
17	26	M	36.0	3.85	0.106	1.2	3.3	0.31	0.11	Active rheumatic fever
18	55	F	43.8	5.42	0.142	1.9	4.3	0.35	0.13	
			44.0	5.40	0.148	1.9	4.3	0.35	0.13	After 4 days of therapy
			43.0	5.51	0.140	1.8	4.2	0.33	0.13	After 20 days of therapy
19	61	M	48.0	4.46	0.160	1.6	3.3	0.34	0.10	
20	67	F	57.0	6.60	0.182	1.8	3.2	0.27	0.10	Pulmonary fibrosis
					Chronic Pulmonary Disease					
21	75	M	51.0	6.82	0.175	1.7	3.3	0.25	0.10	
22	67	M	55.5	6.55	0.187	2.1	3.8	0.32	0.11	
23	63	M	41.5	4.80	0.138	1.9	4.6	0.40	0.14	
24	62	M	47.5	4.85	0.159	1.6	3.4	0.33	0.10	
25	64	M	46.0	5.14	0.138	2.1	4.6	0.41	0.15	
26	74	M	42.0	5.01	0.140	1.5	3.6	0.30	0.11	
27	56	M	47.0	5.30	0.171	1.5	3.2	0.28	0.09	Fibrosis
28	66	M	42.0	4.90	0.137	1.6	3.8	0.33	0.12	Fibrosis
29	67	M	49.0	5.10	0.153	1.7	3.5	0.33	0.11	Fibrosis
30	54	M	60.0	6.23	0.199	2.1	3.5	0.34	0.11	Fibrosis
31	71	M	45.0	5.13	0.154	1.2	2.7	0.23	0.08	Asthma
32	75	M	39.5	4.55	0.136	2.0	5.1	0.44	0.15	Asthma
			41.0	4.16	0.131	1.8	4.4	0.43	0.14	Asthma; 1 year later
33	80	M	52.0	5.39	0.177	1.5	2.9	0.28	0.08	Asthma
34	61	M	39.5	4.13	0.127	1.6	4.0	0.39	0.13	Asthma
35	76	M	50.0	5.60	0.157	1.7	3.4	0.30	0.11	Asthma
36	57	M	57.0	7.16	0.169	2.0	3.5	0.32	0.12	Cor pulmonale and congestive failure
37	46	M	72.0	7.67	0.226	2.3	3.2	0.30	0.10	Cor pulmonale and congestive failure
			66.0	7.45	0.202	2.3	3.5	0.31	0.11	One year later
38	66	M	61.0	6.12	0.198	1.7	2.9	0.29	0.09	Cor pulmonale and congestive failure
39	45	M	75.3	7.74	0.163	2.5	3.5	0.34	0.16	Cor pulmonale and congestive failure
40	66	M	57.8	5.37	0.203	2.2	3.8	0.41	0.11	Cor pulmonale and congestive failure
			56.6	5.59	0.187	2.4	4.2	0.43	0.13	After 3 days
			54.7	5.55	0.164	2.0	3.6	0.37	0.12	After 13 days
			49.0	5.00	0.147	1.9	3.9	0.38	0.13	Pneumonia, a month later
					Superior Vena Caval Thrombosis					
41	28	F	36.0	3.59	0.121	2.0	5.6	0.59	0.17	

MATERIAL AND METHODS

Forty-one patients ranging in age from 28 to 80 were studied: 30 were men. Twenty had moderate to severe exertional dyspnea and mild to moderate dyspnea at rest consequent to chronic congestive

failure. Twenty others had dyspnea due to chronic pulmonary disease; several of the latter had, in addition, chronic congestive failure considered to be consequent to cor pulmonale, while a few had paroxysms of bronchial asthma from time to time (table). One patient had dyspnea and orthopnea as a consequence of obstruction of the superior vena cava apparently due to thrombosis following trauma.

Venous blood was used for the measurements. The hematocrit value, hemoglobin concentration, erythrocyte count and carbonic anhydrase activity were established from the same sample in each case. The carbonic anhydrase activity in each instance was calculated from six measurements, according to a method described elsewhere.[4]

OBSERVATIONS

The values for carbonic anhydrase activity per cubic centimeter of blood, per cubic centimeter of erythrocytes, per gram of hemoglobin and per billion erythrocytes were normal in all cases of chronic congestive failure except cases 11, 14 and 17. In these cases anemia consequent to fever, malnutrition or hemorrhage was present, so that the carbonic anhydrase activities per cubic centimeter of whole blood were somewhat low; however, the values relative to hematocrit levels, hemoglobin levels and erythrocyte counts were normal in these instances.

The carbonic anhydrase activity per cubic centimeter of whole blood was normal in all instances of chronic pulmonary disease; it lay in the upper normal range in the patients in cases 30, 35 and 37, who exhibited polycythemia. In the latter instances, however, the relation of carbonic anhydrase activity to hematocrit values, hemoglobin levels and erythrocyte counts was normal.

The patient with dyspnea consequent to obstruction of the superior vena cava showed normal carbonic anhydrase activity in the blood.

COMMENT

The data of the present study show that in most patients with dyspnea consequent to chronic congestive failure or pulmonary disease each cubic centimeter of blood exhibits normal carbonic anhydrase activity when anemia or polycythemia is not present. The occurrence of anemia due to infection, malnutrition or hemorrhage is associated with decrease in carbonic anhydrase activity in the blood proportional to the lowering in the hematocrit value; polycythemia, on the other hand, is associated with a rise in carbonic anhydrase activity proportional to the hematocrit value. In all instances, therefore, the carbonic anhydrase activity in the blood in relation to hematocrit levels, hemoglobin levels and erythrocyte counts was normal; this phenomenon was noted previously in cases of the common anemias and polycythemia

vera.[5] Accordingly, it is evident that, except in the case of pernicious anemia as noted elsewhere,[5a] the hematocrit value is a useful indicator of carbonic anhydrase activity per unit of blood.

Elevation of hematocrit levels in cases of chronic pulmonary disease is generally regarded as a mechanism compensatory for anoxia; it is to be noted, however, that not only is hemoglobin content increased as a consequence of polycythemia but that carbonic anhydrase activity is also increased. The secondary polycythemia of chronic pulmonary disease is apparently a mechanism which may obviate the effects of both anoxia and hypercarbia. The precise role of carbonic anhydrase in carbon dioxide transport is, however, not established, so that no acceptable interpretation can be made of the effect of polycythemia on the symptoms which might be due to the hypercarbia of pulmonary disease. In one respect, however, speculation may be justified: The fact that the enzyme accelerates the reaction $H_2O + CO_2 \leftrightarrows HCO_3$ suggests that under the conditions of increased speed of blood flow through the tissues and the lungs which obtain in pulmonary disease,[6] increased carbonic anhydrase activity in the blood would be useful. It is possible also that increased carbonic anhydrase activity accounts in part for increased tolerance to inhaled carbon dioxide exhibited by some patients with chronic pulmonary disease.[7]

In uncomplicated chronic congestive failure the carbonic anhydrase activity per unit of blood is normal; the large increase in blood volume in cardiac decompensation with its consequent increase in circulating red cell mass [1] implies a corresponding increase in total circulating carbonic anhydrase. The possible usefulness of this change is not established.

The patient with obstruction of the superior vena cava who showed normal blood carbonic anhydrase levels exemplifies the fact that hyperventilation and mild alkalosis per se which existed over a period of years [8] have no influence on carbonic anhydrase activity in the blood.

5. (*a*) Lewis, H. D., and Altschule, M. D.: Blood Carbonic Anhydrase Activity in Anemia, to be published. (*b*) Hodgson.[2] (*c*) Lambie.[3]

6. McMichael, J., and Sharpey-Schafer, E. P.: The Action of Digoxin in Man, Quart. J. Med. **13**:123, 1944. Richards, D. W., Jr.: Cardiac Output by the Catheterization Technique, in Various Clinical Conditions, Federation Proc. **4**:215, 1945.

7. Reinhardt, R.: Ueber das Verhältniss von CO_2-Ausscheidung zur Atemgrösse beim Lungenemphysem, Deutsches. Arch. f. klin. Med. **109**:192, 1912. Scott, R. W.: The Total Carbonate Content of the Arterial and Venous Plasma in Patients with Chronic Pulmonary Emphysema, Proc. Soc. Exper. Biol. & Med. **17**:21, 1919; Observations on the Pathologic Physiology of Chronic Pulmonary Emphysema, Arch. Int. Med. **26**:544 (Nov.) 1920. Christie, R. V.: Elastic Properties of the Emphysematous Lung and their Clinical Significance, J. Clin. Investigation **13**:295, 1934.

8. Altschule, M. D.; Iglauer, A., and Zamcheck, N.: Respiration and Circulation in Patients with Obstruction of the Superior Vena Cava: Cerebral Factors in Dyspnea and Orthopnea, Arch. Int. Med. **75**:24 (Jan.) 1945.

SUMMARY

Measurements of carbonic anhydrase activity in the blood were made in 40 patients with dyspnea consequent to chronic cardiac or pulmonary disease and in 1 patient with obstruction of the superior vena cava. In all instances the blood carbonic anhydrase level was normal in relation to hematocrit value, erythrocyte count and hemoglobin concentration. The significance of increased carbonic anhydrase activity found in patients with polycythemia associated with pulmonary disease and of the increased total circulating carbonic anhydrase in patients with increased blood volumes consequent to congestive failure is discussed.

Progress in Internal Medicine

GASTROENTEROLOGY

A Review of the Literature from July 1947 to July 1948

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From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago, The School of Medicine.

INTRODUCTION

The present review represents an even more laborious endeavor than in preceding years. Exclusive of those on the liver, the gallbladder, the biliary tract and the pancreas, the number of articles read by the reviewers exceeds 1,600. A considerable proportion merely summarize present knowledge of various gastroenterologic subjects. Many papers have been included for completeness and as an indication of current interests in the field, even though they do not contribute significant new information. Some important publications may have been unintentionally omitted.

The literature, in general, is dominated by technical discussions and by reports of advances in the surgical treatment of cancer of the digestive tract. There is continued dissatisfaction with the diagnosis of early cancer. There is, this year, a pronounced interest in the role of vagotomy in the treatment of peptic ulcer. Peptic ulcer and ulcerative colitis remain subjects of speculation, on which opinions differ. Relatively few fundamental studies have appeared, although an increasing number are devoted to the fascinating phenomenon of gastric secretion. The psychosomatic aspects of gastrointestinal disease are apparently receiving greater attention.

The reviewers now have completed five years of analysis of the gastroenterologic literature; certain comments may therefore be permissible. The quality of the papers, in general, has not kept pace with the tremendous increase in quantity. There is a scarcity of well planned and carefully controlled investigations. Without in any way reflecting on honest differences of opinion, some writers appear to have indulged in unnecessary speculation and unwarranted conclusions. The reviewers sincerely hope for a more critical appraisal of clinical and experimental studies by both authors and editors before publication.

BOOKS ON GASTROENTEROLOGY

Fourteen new books [1] dealing with a variety of gastroenterologic subjects were published during the year; these are listed without com-

1. (*a*) Lickley, J. D.: An Introduction to Gastro-Enterology: A Clinical Study of the Structure and Functions of the Human Alimentary Tube, Baltimore, Williams & Wilkins Company, 1947. (*b*) Vinson P. P.: Diseases of the Esophagus, Springfield, Ill., Charles C Thomas, Publisher, 1947. (*c*) Winkelstein, A.: Modern Treatment of Peptic Ulcer, New York, Oxford University Press, 1948. (*d*) Deller, F. C.: The Modern Management of Gastric and Duodenal Ulcer, Edinburgh, E. & S. Livingstone, 1948. (*e*) Dewberry, E. B.: Food Poisoning, ed. 2, London, Leonard Hill, Ltd., 1948. (*f*) Kinsella, V. J.: The Mechanism of Abdominal Pain, Sydney, Australia, Angus & Robertson, Ltd., 1948. (*g*) Feldman, M.: Clinical Roentgenology of the Digestive Tract, ed. 3, Baltimore, Williams &

(*Footnote continued on next page*)

ment, since they have been reviewed elsewhere. Attention may be directed, however, to Vinson's summary of "Diseases of the Esophagus,"[1b] to Winkelstein's "Modern Treatment of Peptic Ulcer,"[1c] to Dewberry's discussion of "Food Poisoning,"[1e] and to the excellent texts on the roentgenologic features of gastrointestinal diseases by Feldman[1g] and by Buckstein.[1h] Dunbar's "Mind and Body"[1i] should interest gastroenterologists particularly. "The Surgical Treatment of the Abdomen," by Bancroft and Wade,[1j] and "The Surgery of the Colon and Rectum," by the Devines,[1k] also contain a wealth of information. The fourth edition of Gutmann's treatise on painful syndromes of the epigastric region[1l] is well illustrated, containing reproductions of 962 roentgenograms; however, exception may be taken to the validity of several syndromes discussed by the author. Two of the new books, Arias Vallejo's study of disturbances in gastric emptying[1m] and Gutiérrez Blanco's review of chronic ulcerative colitis,[1n] are in Spanish.

THE ESOPHAGUS

General Matter.—Benedict[2] and Nagel[3] present general discussions of the diagnosis and treatment of esophageal diseases. Holinger and his associates[4] describe the camera and the technic employed by them in bronchoscopic and esophagoscopic cinematography; their film is an outstanding portrayal of esophageal diseases.

Esophageal Atresia and Tracheoesophageal Fistula.—Wright[5] discusses the embryologic, anatomic and surgical aspects of congenital esophageal atresia. Perrone and his associates[6] report 6 fatal cases. The

Wilkins Company, 1948. (*h*) Buckstein, J.: The Digestive Tract in Roentgenology, Philadelphia, J. B. Lippincott Company, 1948. (*i*) Dunbar, H. F.: Mind and Body: Psychosomatic Medicine, New York, Random House, Inc., 1948. (*j*) Bancroft, F. W., and Wade, P. A.: Surgical Treatment of the Abdomen, Philadelphia, J. B. Lippincott Company, 1947. (*k*) Devine, H., and Devine, J.: The Surgery of the Colon and Rectum, Bristol, England, John Wright & Sons, Ltd., 1948. (*l*) Gutmann, R. A.: Les syndrome douloureux de la région épigastrique, ed. 4, Paris, Gaston Doin & Cie, 1947, vols. 1 and 2. (*m*) Arias Vallejo, A.: Disfunciones motoras del estomago, Madrid, Eraficas Valera, 1947. (*n*) Gutiérrez Blanco, H.: Colitis ulcerosa crónica, Montevideo, Uruguay, A. Manteverde y Cia, 1947.

2. Benedict, E. B.: Medical Progress: Endoscopy, New England J. Med. **237**:92, 1947; Endoscopy, S. Clin. North America **27**:1191, 1947.

3. Nagel, G. W.: Lesions of the Esophagus: Diverticulum, Cardiospasm, Megaesophagus and Cancer, M. Clin. North America **32**:363, 1948.

4. Holinger, P. H.; Anison, G. C., and Johnston, K. C.: Bronchoscopic and Esophagoscopic Cinematography, J. Thoracic Surg. **17**:178, 1948.

5. Wright, H. S.: Congenital Esophageal Atresia, Canad. M. A. J. **57**:237, 1947.

6. Perrone, J. A.; Fleming, W. H., and Whitaker, T. R.: Congenital Atresia of the Esophagus with Tracheoesophageal Fistula, Arch. Otolaryng. **46**:608 (Nov.) 1947.

surgical treatment of the condition is considered by Sandblom,[7] and by a number of other writers: Rienhoff [8] describes a technic for the subcutaneous implantation of the stomach in the chest wall, utilized in the treatment of esophageal atresia in 2 infants. Four patients with esophageal atresia and tracheoesophageal fistula were successfully treated by ligation of the fistula and primary anastomosis of the esophagus.[9] Two similar cases are reported from England [10]; according to the author, these apparently represent the first successful treatment of these conditions in that country. In another series, 1 of 4 infants withstood the operative procedure and was alive and well at the time of writing; 2 infants had been born prematurely and were poor operative risks.[11] A new method of restoring continuity of the alimentary canal in cases of congenital atresia of the esophagus with tracheoesophageal fistula in which patients are not treated by immediate primary anastomosis is presented by Sweet.[12]

Diverticula.—The subject is discussed generally by Ramos Mejia.[13] King [14] states the belief that pharyngoesophageal diverticula develop when the cricoid cartilage of the mature larynx, pressing against the vertebrae, produces an area of weakness in the musculature of the posterior wall of the pharynx. Wheeler [15] points out that with the exception of the pharyngoesophageal type, diverticula of the esophagus are usually incidental findings and ordinarily do not cause symptoms. In 1 case,[16] a diverticulum was resected successfully, but the digestive

7. Sandblom, P.: Surgical Treatment of Esophagus Atresia, Nord. med. **38**:787, 1948.

8. Rienhoff, W. F., Jr.: Antethoracal Transplantation of the Stomach in the Treatment of Congenital Atresia of the Thoracic Esophagus, Bull. Johns Hopkins Hosp. **82**:496, 1948.

9. Longmire, W. P., Jr.: Congenital Atresia and Tracheoesophageal Fistula: Four Consecutive Cases of Successful Primary Esophageal Anastomosis, Arch. Surg. **55**:330 (Sept.) 1947.

10. Franklin, R. H.: Congenital Atresia of the Esophagus: Two Cases Successfully Treated by Anastomosis, Lancet **2**:243, 1947.

11. Lyon, C. G., and Johnson, S. G.: Congenital Esophageal Atresia and Tracheoesophageal Fistula, J. Thoracic Surg. **17**:162, 1948.

12. Sweet, R. H.: A New Method of Restoring Continuity of the Alimentary Canal in Cases of Congenital Atresia of the Esophagus with Tracheoesophageal Fistula Not Treated by Immediate Primary Anastomosis, Ann. Surg. **127**:757, 1948.

13. Ramos Mejía, M. M.: Diverticula of the Esophagus, Prensa méd. argent. **34**:1683, 1947.

14. King, B. T.: New Concepts of the Etiology and Treatment of Diverticula of the Esophagus, Surg., Gynec. & Obst. **85**:93, 1947.

15. Wheeler, D.: Diverticula of the Foregut, Radiology **49**:476, 1947.

16. Forrester-Wood, W. R.: Epiphrenic Diverticulum of the Esophagus, Brit. J. Surg. **35**:418, 1948.

symptoms persisted. A dissecting form of pharyngoesophageal diverticulum in a boy of 15 is described.[17]

Duplications.—Jones[18] discusses the histology, embryology, symptomatology, diagnosis and treatment of esophageal duplications and of mediastinal cysts of enteric origin. This type of cyst lies posteriorly and retropleurally, is most common on the right side and frequently is accompanied with other anomalies. It is lined with esophageal or gastric mucosa and is covered with two layers of muscular wall. The cyst frequently contains acid gastric juice; an active peptic ulcer has been observed in a cyst, with perforation into the pleura and lungs. The lesion may be present without symptoms, but it commonly causes pneumonia and pleural effusion, early in life; atelectasis, obstructive emphyema and dyspnea may occur. Lateral and oblique roentgenograms of the thorax reveal the cyst to lie posteriorly, in contrast to dermoid cysts, teratomas and pericardial cysts. The treatment of choice is complete surgical removal. In the 2 cases reported by the author, 1 patient died without operation. The second patient recovered after surgical treatment; gastric mucosa was present in the cyst. Davidson and Brown[19] describe a gastrogenous cyst of the mediastinum. A congenital intrathoracic gastric cyst, in a girl of 14, was successfully removed.[20] An enterogenous cyst containing gastric mucosa was removed from the chest of a male infant of 22 months, who recovered.[21]

Esophagitis and Peptic Ulcer.—Olsen[22] points out that although esophagitis may be the most frequent disease of the esophagus, it is seldom recognized during life. Etiologic factors include the prolonged use of a nasal tube, reflux of gastric secretion into the esophagus, protracted vomiting and possibly hiatus hernia and brain tumor. Esophagitis is not uncommon after abdominal surgery.

Allison[23] discusses 74 instances of peptic ulcer of the esophagus. The most prominent symptom was dysphagia, which was more pronounced for solid foods than for liquids. "Dyspepsia" was present in approximately three fourths of the patients, as (*a*) epigastric discomfort associated with high acid secretion, (*b*) burning retrosternal pain,

17. Melamed, A., and Walker, L. J.: Dissecting (Intramural) Pharyngo-Esophageal Diverticulum, Radiology **49**:712, 1947.

18. Jones, J. C.: Esophageal Duplications or Mediastinal Cysts of Enteric Origin, West. J. Surg. **55**:610, 1947.

19. Davidson, L. R., and Brown, L.: Gastrogenous Mediastinal Cyst, J. Thoracic Surg. **16**:458, 1947.

20. Davis, E. W., and Salkin, D.: Intrathoracic Gastric Cysts, J. A. M. A. **135**:218 (Sept. 27) 1947.

21. Christofferson, J. C.: Intrathoracic Gastric Cyst, Acta chir. Scandinav. **96**:12, 1947.

22. Olsen, A. M.: Esophagitis, editorial, Surg., Gynec. & Obst. **86**:372, 1948.

23. Allison, P. R.: Peptic Ulcer of Esophagus, Thorax **3**:20, 1948.

attributable to acid bathing the lower end of the inflamed esophagus, or (*c*) a more boring type of pain, extending to the back between the shoulder blades and often made worse by flexion of the spine. Heterotopic gastric mucosa in the esophagus accounted for a few instances. Congenitally short esophagus was not encountered. A defect in the diaphragm, congenital or acquired, is considered the most important etiologic factor. Such a defect allows herniation of the cardia into the mediastinum and thereby renders ineffective the mechanism for keeping acid out of the esophagus. The hernia may be congenital, infantile or acquired. In 4 patients, esophageal ulceration developed after excision of a carcinoma of the cardia and gastroesophageal anastomosis. In another case,[24] oxycel gauze® applied topically was successful in controlling the hemorrhage arising in a peptic ulcer of the esophagus.

A man of 20, who had sustained a head injury at birth, presented the symptoms of epilepsy, repeated vomiting, hematemesis, melena and anemia. Resection of the scarred esophagus, containing a peptic ulcer, and resection of the thoracic portion of the herniated stomach are reported to have relieved the symptoms completely, including the epileptic seizures.[25]

After resection of a carcinoma of the cardia and performance of gastroesophagostomy, a patient died of massive hemorrhage.[26] Autopsy revealed an ulceration at the anastomosis, penetrating into the aorta; the lesion was attributed to the digestive action of acid in the gastric content.

Stricture.—The role of esophagitis in the pathogenesis of cicatricial contraction of the esophagus is emphasized by Schmidt.[27] Mechanical dilation is preferred to resection and anastomosis. Bryan[28] notes the development of agranulocytosis after sulfadiazine therapy for peritonsillar abscess, followed with ulceration and then with stenosis of the esophagus. A case of acquired stricture of the esophagus, with esophagobronchial fistula and bronchiectasis of the entire right lung, is reported.[29]

24. Castleton, K. B., and Dolowitz, D. A.: Peptic Ulcer of the Esophagus with Severe Bleeding Controlled by Oxycel, Gastroenterology **10**:797, 1948.

25. Wright, A. D.: Congenital Short Esophagus, Proc. Roy. Soc. Med. **41**:378, 1948.

26. Maguire, W. C., and Mitchell, N.: Perforation of the Aorta by Acid Gastric Contents at Site of Gastroesophagostomy, Surgery **22**:842, 1947.

27. Schmidt, H. W.: Cicatricial Stricture of the Esophagus, Proc. Staff Meet., Mayo Clin. **23**:265, 1948.

28. Bryan, B. D.: Esophageal Stricture Following Agranulocytosis Due to Sulfonamide Therapy, New England J. Med. **237**:941, 1947.

29. Clagett, O. T., and Schmidt, H. W.: Surgical Management of Acquired Stricture of the Esophagus with Esophagobronchial Fistula and Bronchiectasis of Entire Right Lung, Surgery **23**:221, 1948.

In the treatment of injuries of the esophagus due to lye, Blassingame and his associates [30] recommend prompt neutralization with weak acid, frequent feedings of cream and oil, thorough pharyngeal and esophageal examination and daily antegrade dilations of the esophagus with mercury-filled or lead-filled bougies. The importance of esophageal dilations as early as the third or fourth day after ingestion of the caustic substance is emphasized by Latorre Agüero [31] and by Rassudov.[32]

Kernodle and associates,[33] on the basis of experience with 136 cases of lye burns of the esophagus in children, advise the immediate administration of weak acid, such as dilute vinegar or lemon or orange juice. The use of weighted rubber catheters is recommended, beginning on the fourth day after the injury. Two patients with esophageal stricture after the ingestion of caustic agents were successfully treated by mechanical dilation.[34]

Partial esophageal resection with end to end reconstruction is recommended when the stenosis involves a short segment of the esophagus and does not respond readily to the usual methods of dilation; an illustrative case is described.[35] Four patients with stricture after the ingestion of lye were managed effectively by resection of the involved segment.[36] Partial esophagectomy was performed in a patient with a benign stricture located high in the esophagus.[37]

Perforations and Wounds.—Four instances of perforation of the esophagus into the mediastinum and/or the pleural cavity are described.[38] In 2, the etiologic factors were peptic ulcer of the lower end of the esophagus and cardioesophageal junction. Perforation occurred in 1

30. Blassingame, C. D.; McArthur, R. H., and Atkinson, R. H.: Ingestion of Lye—a Serious Problem, South. Surgeon **13**:626, 1947.

31. Latorre Agüero, A.: Esophageal Stenosis Due to Caustics, Rev. otorrinolaring. **7**:81, 1947.

32. Rassudov, P. M.: Early Treatment of Esophageal Burns in Children, Am. Rev. Soviet Med. **5**:101, 1948.

33. Kernodle, G. W.; Taylor, G., and Davison, W. C.: Lye Poisoning in Children, Am. J. Dis. Child. **75**:135 (Feb.) 1948.

34. Señorans, A. J.; Goñi, I., and Fromm, G. A.: Treatment of Stricture of the Esophagus Following the Ingestion of Caustics, Arch. argent. de enferm. d. ap. digest. y de la nutrición **22**:96, 1947.

35. Gross, R. E.: Treatment of Short Stricture of the Esophagus by Partial Esophagectomy and End-to-End Esophageal Reconstruction, Surgery **23**:735, 1948.

36. Puestow, C. B., and Chess, S. J.: Resection of the Esophagus for Persistent Stricture, Arch. Surg. **56**:34 (Jan.) 1948.

37. Donald, C. J., and Kessler, C. H.: Subtotal Esophagectomy for Benign Stricture of the Esophagus, South. M. J. **41**:26, 1948.

38. Culver, G. J., and Clark, S. B.: The Radiographic Diagnosis of Perforations of the Upper Gastrointestinal Tract Into the Mediastinum and Pleural Cavity, Surgery **22**:458, 1947.

case after dilation of the esophagus for cardiospasm and in another after esophagoscopy. Three patients died shortly after the onset of symptoms. The roentgenologic demonstration of hydropneumothorax in a patient who experiences sudden onset of thoracic or abdominal pain, accompanied by shock and collapse, is considered diagnostic of a perforation of the upper part of the gastrointestinal tract into the mediastinum and pleural cavity.

Perforations of the posterior portion of the esophageal wall at the level of the cricoid cartilage are reported after gastroscopy and esophagoscopy, respectively.[39] The main intrinsic predisposing factor seems to be anterior prominence of the extended cervical portion of the spine, particularly when the spine is roughened by the osteophytes of spondylitis; a routine roentgenogram of the cervical portion of the spine is therefore recommended. The correct treatment consists of immediate suture of the perforation, drainage and the use of sulfonamide and antibiotic drugs. Dorsey [40] discusses the surgical management of esophageal perforation with suppurative mediastinitis and presents 4 cases in which treatment was successful. A patient with an apparently spontaneous perforation of the esophagus recovered after surgical intervention.[41] Sommer and O'Brien [42] report 2 instances of war wounds of the esophagus and emphasize the need for prompt surgical intervention.

Varices.—Among 115 patients with esophageal varices, hematemesis was the presenting symptom of 70 per cent; 84 per cent of the latter group died of hemorrhage shortly after admission to the hospital. A history of previous hemorrhage was obtained in 22 per cent of cases. The excessive ingestion of alcoholic beverages was noted in 61 per cent. Cirrhosis of the liver was diagnosed clinically or at autopsy in 80 per cent.[43] In another study,[44] varices involving the fundus of the stomach simulated a tumor.

Twelve of 22 patients treated for esophageal varices by injection with a sclerosing solution (5 per cent sodium morrhuate) had not experienced further bleeding for more than three years at the time of

39. Goligher, J. C.: Postcricoid Pharyngo-Esophageal Perforation Due to Endoscopy, Treated by Immediate Suture, Lancet **1**:985, 1948.

40. Dorsey, J. M.: Surgical Treatment of Perforation of the Esophagus, Arch. Surg. **56**:24 (Jan.) 1948.

41. Barrett, N. R.: Report of a Case of Spontaneous Perforation of the Esophagus Successfully Treated by Operation, Brit. J. Surg. **35**:216, 1947.

42. Sommer, G. N. J., and O'Brien, C. E.: War Wounds of the Esophagus, J. Thoracic Surg. **7**:393, 1948.

43. Higgins, W. H.: The Esophageal Varix, Am. J. M. Sc. **214**:436, 1947.

44. Hare, H. F.; Silveus, E., and Ruoff, F. A.: Esophageal and Gastric Varices, with Report of a Case, S. Clin. North America **28**:729, 1948.

writing.[45] The results were not satisfactory in cases of concomitant varices in the cardiac end of the stomach.

Patterson and Rouse [46] present a follow-up report on 26 patients, from 3 to 66 years of age, with hematemesis arising in esophageal varices. Two patients not treated with sclerosing solutions died of hemorrhage. Of the 24 patients who received one or more sclerosing injections, 9 died; 6 of the deaths were the result of esophageal bleeding and 3 were due to other causes. A decrease in the incidence of recurrent hemorrhage was observed after injection therapy in the remaining cases; 1 patient in this group was a child of 3.

Posterior mediastinostomy was successful in controlling the bleeding in 2 patients with recurrent hematemesis.[47] One patient had been free of hemorrhage for six years at the time of writing and the other, for fourteen months. It is assumed that the irritation from the packing promoted the growth of granulation tissue and the establishment of a new vascular network between the submucosal and periesophageal veins of the esophagus and the deeper venous channels of the mediastinum. A new and different technic is the insertion of a latex bag, attached to a Miller-Abbott tube, into the lower end of the esophagus.[48] In the reported case, the device was left in place for four days after inflation with 120 cc. of air. The tamponade proved to be a life-saving measure.

Cardiospasm.—Suermondt [49] attributes this disorder to failure of the reflex opening of the cardia, mediated by the sympathetic nerves; he suggests resection of the sympathetic fibers. To the best of our knowledge, the procedure has not received a thorough trial in man. It may be of interest, in this connection, to investigate the possible therapeutic effects of dibenamine® (N, N-dibenzyl-beta-chloroethylamine) or of other inhibitors of function of the sympathetic nerve fibers.

In 63 per cent of a group of pigeons with beriberi, induced by a special diet of rice, dilatation of the esophagus developed.[50] The author regards deficiency of thiamine as an etiologic factor in some instances of achalasia. A case is presented in which achalasia developed after

45. Moersch, H. J.: Treatment of Esophageal Varices by Injection of a Sclerosing Solution, J. A. M. A. **135**:754 (Nov. 22) 1947.

46. Patterson, C. O., and Rouse, M. O.: The Sclerosing Therapy of Esophageal Varices, Gastroenterology **9**:391, 1947.

47. Som, M. L., and Garlock, J. H.: New Approach to the Treatment of Esophageal Varices, J. A. M. A. **135**:628 (Nov. 8) 1947.

48. Rowntree, L. G.; Zimmerman, E. F.; Todd, M. H., and Ajac, J.: Intra-esophageal Venous Tamponage: Its Use in a Case of Varical Hemorrhage from the Esophagus, J. A. M. A. **135**:630 (Nov. 8) 1947.

49. Suermondt, W. F.: De achalasia van de cardia, Nederl. tijdschr. v. geneesk. **91**:1689, 1947.

50. Simonetti, C.: Achalasia del cardias do B_1 avitaminosei, Ann. ital. di chir. **24**:137, 1947.

severe pertussis [51]; the author speculates on the possibility of "toxic" damage to a portion of Auerbach's plexus.

Templeton [52] found that the muscular action of the esophagus in achalasia differs from the normal. In 36 of 39 patients, the primary wave, instead of proceeding the entire length of the esophagus, as it does normally, ceased at approximately the level of the suprasternal notch or the superior margin of the aortic arch. The portion of the esophagus over which the wave passed remained contracted for a second or two. When it relaxed, the content of the esophagus flowed upward but was prevented from entering the pharynx by the contracted cricopharyngeous muscle. Secondary waves were not observed. In all but 2 patients, purposeless, shallow, segmental contractions constantly appeared and disappeared at different levels of the esophagus. These undulating movements were also accompanied by generalized tonic contractions, diffusely narrowing the esophageal lumen. When amyl nitrite was administered to the supine patient, all action of the esophageal muscles ceased; the lumen enlarged, and the margins became smooth. The author suggests that cardiospasm (achalasia) is a disorder of the muscular portion of the esophagus proper and not of the cardia, and that the disease, in some manner, destroys the propagating mechanism of the peristaltic wave: In the advanced stage there is an associated pronounced loss of tone and dilatation of the esophagus.

An instance of chronic pulmonary infection caused by aspiration of the contents of the dilated esophagus is reported.[53] The diagnostic features and treatment of cardiospasm are reviewed by Roux.[54] Ceranke [55] found sodium nitrate, administered subcutaneously, of value in the treatment of 3 female patients. Massion [56] emphasizes dilation with mercury-laden sounds.

Sweet [57] states that whereas many patients with idiopathic dilatation of the esophagus are maintained relatively symptom free by conservative

51. Cunha, F.: Achalasia and Megaesophagus as a Complication and Sequela of Pertussis, Rev. Gastroenterol. **14**:693, 1947.

52. Templeton, F. E.: Movements of the Esophagus in the Presence of Cardiospasm and Other Esophageal Diseases, Gastroenterology **10**:96, 1948.

53. Heaton, T. G.: Cardiospasm with Associated Pulmonary Disease, Dis. of Chest **14**:425, 1948.

54. Roux, M.: Diagnostic clinique et indications thérapeutiques du mégaœsophage, Presse méd. **56**:424-B (June 16, supp.) 1948.

55. Ceranke, P.: Die idiopathische Oesophagusdilatation und ihre Beeinflussung durch Nitrokörper, Wien. klin. Wchnschr. **59**:681, 1947.

56. Massion, J.: Remarques sûr le megaesophage et le traitement par la sonde à mercure, Acta gastroenterol. belg. **11**:101, 1948.

57. Sweet, R. H.: Idiopathic Dilatation of the Esophagus, S. Clin. North America **27**:1128, 1947.

measures, the degree of obstruction in some persons is so severe as seriously to impair their health. An adaptation of the Heineke-Mikulicz procedure, consisting of a longitudinal incision with circumferential closure of the pathologically narrowed segment, was employed in 14 patients and resulted in relief of symptoms and some decrease in the size of the esophagus. Seventeen patients were treated by transpleural cardioplasty [58]; in each case, there was relief of symptoms and a pronounced reduction in the size of the esophagus. In 8 cases of cardiospasm,[59] treatment was by esophagogastrostomy. Most patients continued to manifest some symptoms referable either to the process of swallowing or to the upper part of the gastrointestinal tract; otherwise, their condition had definitely improved. The appearance of the esophagus returned to normal in 5 cases and improved in 1.

Miscellaneous Conditions.—The intravenous administration of iron is recommended in the treatment of the Plummer-Vinson syndrome.[60] Esophageal obstruction in 1 case [61] resulted from herniation of gastric mucosa into the esophagus. The diagnosis was established by microscopic examination of a specimen for biopsy obtained at esophagoscopy. The patient recovered spontaneously after sixteen days and remained well during the one year follow-up period. In a patient with sclerodactyly,[62] visceral lesions were present in the esophagus and pericardium, and probably also in the heart muscle and the pleura. A fatal case of diphtheria is reported [63] in a female infant of 1 month, in whom the entire esophagus and the cardiac orifice of the stomach were involved in the diphtheritic process. In another case,[64] an upper denture, lodged 7 cm. above the diaphragm, was removed from the patient's esophagus with a forceps operated through a sigmoidoscope introduced into a gastrostomy opening.

In 8 cases, aortic aneurysm produced clinical features resembling carcinoma of the esophagus, disease of the biliary tract, gastric car-

58. Kay, E. B.: Surgical Treatment of Cardiospasm, Ann. Surg. **127**:34, 1948.

59. Gill, D. C., and Child, C. G., III: Esophagogastrostomy in the Treatment of Cardiospasm, Surgery **23**:571, 1948.

60. Lederer, J., and Renoer, M.: Le syndrome de Plummer-Vinson et son traitement par la thérapeutique martiale parentérale, Acta gastroenterol. belg. **11**:71, 1947.

61. Wells, J.: Herniation of Gastric Mucosa Into the Esophagus, Am. J. Roentgenol. **58**:194, 1947.

62. Bourne, W. A.: Sclerodactylia with Esophageal Lesion, Proc. Roy. Soc. Med. **41**:43, 1948.

63. Hoyne, A. L.: Diphtheria of the Esophagus: Case Involving Stomach and Tongue, Am. J. Dis. Child. **74**:80 (July) 1947.

64. Gatch, W. D., and Molt, W. F.: Transgastric Removal of Large Solid Bodies Impacted in the Lower Part of the Esophagus, Arch. Surg. **56**:21 (Jan.) 1948.

cinoma, peptic ulcer or mesenteric thrombosis. Displacement of the esophagus to the left and anteriorly is considered almost diagnostic of aneurysm at the diaphragmatic hiatus.[65]

In 3 patients with primary bronchopulmonary cancer, the clinical features simulated those of esophageal stenosis, with an absence of bronchopulmonary symptoms.[66]

Tumors.—Esophageal polyps,[67] polypoid tumors,[68] an angioma of the esophagus [69] and a leiomyoma involving both the esophagus and the stomach [70] are reported.

Carcinoma.—The clinical features of carcinoma of the esophagus and the difficulties in diagnosis are discussed by Doyle [71] and by Adams.[72] A carcinoma of the thoracic portion of the stomach was observed in a woman of 49 with a diaphragmatic hernia attributed to a congenitally short esophagus.[73] The patient underwent repair of the hernia for the relief of heartburn and pain in the lower left portion of the chest; the symptoms recurred, and two months later a second operation revealed the neoplasm. The lesion was resected successfully, and continuity restored, by esophagogastric anastomosis. A carcinoma of the esophagus was discovered in a patient with cardiospasm.[74] The histologic characteristics of carcinoma of the esophagus are reviewed in detail [75] on the basis of a study of 26 surgical specimens and 11 tumors removed at autopsy.

The continued progress in the surgical management of esophageal carcinoma is reflected in the large number of papers devoted to the

65. Baer, S., and Loewenberg, S. A.: Aortic Aneurysms Simulating Organic Disease of the Gastro-Intestinal Tract, Gastroenterology **10**:617, 1948.

66. Llámbes, J., and Moreno, R.: La forma esofágica del cáncer broncopulmonar, Prensa méd. argent. **35**:130, 1948.

67. Bello, N. J., and Ramos-Mejía, M. M.: Pólipos del esóphago, Arch. argent. de enferm. d. ap. digest. y de la nutrición **22**:341, 1947. Mikhelovich, M. S.: Polyps of the Esophagus, Am. Rev. Soviet Med. **5**:105, 1948.

68. Tanew, N.: Diagnosis of Polypoid Esophageal Tumors, Wien. klin. Wchnschr. **59**:745, 1947.

69. Giuffrida, E.: Angioma of Esophagus, Minerva med. **38**:90, 1947.

70. Kenworthy, R. A., and Welch, C. S.: Leiomyoma of the Esophagus and Cardia of the Stomach, Surgery **23**:745, 1948.

71. Doyle, L.: Carcinoma of Esophagus and Cardiac End of Stomach, Australia & New Zealand J. Surg. **17**:16, 1947.

72. Adams, W. E.: Carcinoma of the Esophagus and Cardia, Nebraska M. J. **32**:381, 1947.

73. Mailer, R.: Carcinoma in a Thoracic Stomach (Congenital Short Esophagus), Brit. J. Surg. **35**:126, 1948.

74. Baer, P., and Sicker, K.: The Association of Achalasia of the Cardia with Esophageal Carcinoma, Brit. J. Radiol. **20**:528, 1947.

75. Gauthier-Villars, P., and Dontzoff, A.: Microscopic Anatomy of Cancer of the Esophagus, Presse méd. **55**:609, 1947.

problem, emanating from all parts of the world.[76] Varying modifications in technic are described by different surgeons; the procedure of choice is apparently transthoracic resection with esophagogastrostomy. According to Maier,[77] the significant decreases in morbidity and mortality rates during the past decade are attributable to better preoperative preparation of the patient, improvements in anesthesia, use of chemotherapy, a better understanding of the physiologic alterations during and after operation, improved surgical technic and better care.

Sweet[78] reviews in detail the results of surgical treatment in 213 cases of carcinoma of the espohagus and the cardiac end of the stomach. Resection and esophagogastric anastomosis were performed in 141 cases (66.2 per cent) and exploration only, in 72. Among the 141 patients receiving definitive treatment, there were 23 deaths (a mortality rate of 16.3 per cent). Complications included cardiac disorders in 33 cases, pulmonary disturbances in 11, empyema in 7 and vascular disorders in 5. An appreciable number of patients had survived for more than two two years at the time of writing. Nine of 23 patients who had an opportunity to survive were alive three or more years after operation. The findings suggest that when the patient survives for three years his chances of further survival, and possibly of cure, are reasonably good. In a later report, Sweet[79] reports a mortality rate of 15.9 per cent among 198 patients undergoing resection. The incidence of postoperative complications decreased as experience in dealing with the problem increased.

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76. Souttar, H. S.: Recent Advances in the Treatment of Carcinoma of the Esophagus, Ann. Roy. Coll. Surgeons England **1**:85, 1947. Eerland, L. D.: Observations on Transthoracic Esophagectomy in Cancer of the Esophagus, Bruxelles méd. **27**:1839, 1947. Magendie, J.: Present Surgical Treatment in Cancer of the Esophagus, Sud. méd. et chir. **79**:255, 1947. Brown, C. J.: Surgical Treatment of Carcinoma of the Esophagus, with Report of Three Cases, M. J. Australia **2**:10, 1947. Wookey, H.: Surgical Treatment of Carcinoma of the Hypopharynx and Esophagus, Brit. J. Surg. **35**:249, 1948. Garlock, J. H.: Progress in the Surgical Treatment of Carcinoma of the Esophagus and Upper Stomach, Surgery **23**:906, 1948. Payne, J. H., and Clagett, O. T.: Transthoracic Gastric Resection for Lesions of Cardia of Stomach and Lower Part of Esophagus, ibid. **23**:912, 1948. Kinsella, T. J.: Carcinoma of the Esophagus, Minnesota Med. **31**:679, 1948. Holst, J.: Thoraco-Abdominal and Transthoracic Resection of the Stomach and Esophagus for Carcinoma, Nord. med. **37**:620, 1948.

77. Maier, H. C.: Preoperative, Operative, and Postoperative Care in Esophageal Resections, Surgery **23**:884, 1948.

78. Sweet, R. H.: Carcinoma of the Esophagus and the Cardiac End of the Stomach: Immediate and Late Results of Treatment by Resection and Primary Esophagogastric Anastomosis, J. A. M. A. **135**:485 (Oct. 25) 1947.

79. Sweet, R. H.: The Treatment of Carcinoma of the Esophagus and Cardiac End of the Stomach by Surgical Extirpation, Surgery **23**:952, 1948.

Thorek [80] reports 22 cases of carcinoma of the esophagus; the lesion was not resectable in 10. Radical resection and intrathoracic esophagogastric anastomosis were performed in 12 cases; in 3 of these the patients died of congestive heart failure, and 9 patients were living at the time of the report. In a series of 71 patients operated on for carcinoma of the esophagus located at or below the arch of the aorta and for carcinoma of the cardiac end of the stomach,[81] the rate of resectability was 65 per cent and the mortality rate, 38.2 per cent. In another series,[82] 6 of 14 patients with cardioesophageal cancer survived radical resection, the average period at the time of the report being thirteen months.

Mason [83] analyzes the results of surgical treatment of various obstructive lesions of the esophagus. Transabdominal esophagogastrostomy was successful in 3 patients with cardiospasm, and in 1 with cicatricial stenosis of the terminal end of the esophagus. A carcinoma of the cardia of the stomach was successfully resected by the transthoracic route. Partial esophagectomy with intrathoracic esophagogastrostomy is advocated for obstructive lesions of the esophagus; however, 2 of 3 patients so treated did not survive. A patient with a stricture of the cervical portion of the esophagus due to lye recovered after external longitudinal division of the stricture and reconstruction of the lumen over a bougie.

Longmire [84] states the belief that unfavorable arrangement of the primary mesenteric vessels to the first portion of the jejunum may make it impossible, at times, to obtain a sufficient length of intestine to reach above the level of the esophageal obstruction. Anastomosis of one of the primary mesenteric arteries and veins to the internal mammary artery and vein insures an adequate blood supply to the mobilized intestine. An illustrative case is described. Experimental work on dogs [85] indicated that the atrophy and absorption of segments of jejunum used in constructing an antethoracic esophagus were due to lack of blood supply; the difficulty may be overcome by interrupting the blood supply in stages.

80. Thorek, P.: Surgical Treatment for Carcinoma of the Esophagus, Illinois M. J. **92**:329, 1947.

81. Strieder, J. W.: Surgical Management of Carcinoma of the Lower Two-Thirds of the Esophagus and Cardiac End of the Stomach, J. Thoracic Surg. **17**:143, 1948.

82. De Amesti, F., and Otaiza, E.: Cardioesophageal Cancers Treated via the Transthoracic and Transdiaphragmatic Route, Surgery **23**:921, 1948.

83. Mason, J. M., III: The Surgical Treatment of Obstructive Lesions of the Esophagus, Ann. Surg. **127**:1067, 1948.

84. Longmire, W. P.: Modification of the Roux Technique for Antethoracic Esophageal Reconstruction, Surgery **22**:94, 1947.

85. Prohaska, J. V., and Sloan, J.: The Use of the Jejunum in the Construction of an Antethoracic Esophagus, Surgery **22**:191, 1947.

Eleven cases of esophagoplasty are reported, with 2 deaths.[86] The use of a tube of skin and a segment of jejunum connecting the dermic tube to the proximal small intestine and bypassing the stomach is considered an improvement over a tube of skin connecting the upper esophagus to the stomach: Reflux of irritating gastric juice is obviated; strictures and fistulas are less common. Reconstruction of an antethoracic esophagus is discussed further by Jeker.[87]

Progress is also being made in the surgical treatment of lesions located high in the esophagus.[88] Two illustrative cases are described by DeBakey and Ochsner.[88a]

Cancer of the cervical portion of the esophagus differs somewhat from cancer of the lower portions of the esophagus in that it occurs at an earlier age and is more common in women.[88c] Squamous cell cancer is more frequent than adenocarcinoma. Of 72 patients, 22 per cent had metastases to the cervical lymph nodes at the time of admission to the hospital. If discovered reasonably early, the disease can be cured surgically; even when it is advanced, with cervical metastases, control may be obtained by aggressive surgery and substantial irradiation. Two patients with advanced cancer of the cervical portion of the esophagus so treated were alive and well ten and ten and a half years after operation, respectively. One patient underwent surgical extirpation of the cancer followed with the reconstruction of a skin-lined, tubular esophagus and seven years later, at the time of the report, was alive and apparently free of the disease.

Fleming [89] points out that although cure is rare after radiotherapy for esophageal cancer, it offers a method of treatment still worth while in many cases beyond the scope of surgical treatment. Freid [90] reviews roentgenologic treatment with reference to technics, factors governing the response to roentgen radiation, complications and results. All of 13 patients treated died; the lesion involved the upper part of the esophagus in 3, the midde part in 5 and the lower part in 5. The time from treatment to death averaged eleven months. There was no evidence of carcinoma in 3 of 4 bodies on which autopsy was performed, and only

86. Swenson, O.: Anterior Thoracic Esophagus, Am. J. Surg. **74**:69, 1947.

87. Jeker, L.: Beitrag zur antethorakalen Oesophagusplastik, Schweiz. med. Wchnschr. **77**:742, 1947.

88. (*a*) DeBakey, M. E., and Ochsner, A.: Subtotal Esophagectomy and Esophagogastrostomy for High Intrathoracic Esophageal Lesions, Surgery **23**:935, 1948. (*b*) Wilton, J.: Total Esophagectomy for Carcinoma of the Middle Third of the Esophagus, South African M. J. **21**:944, 1947. (*c*) Watson, W. L., and Pool, J. L.: Cancer of the Cervical Esophagus, Surgery **23**:893, 1948.

89. Fleming, J. A. C.: Radiotherapy in Cancer of the Thoracic Esophagus, Thorax **2**:206, 1947.

90. Freid, J. R.: Roentgen Treatment of Cancer of the Esophagus, Am. J. Roentgenol. **59**:551, 1948.

a few degenerating cancer cells were present in the fourth patient. One patient was living and well seven and a half years after irradiation. Complications after therapy include damage to the lungs due to radiation, scar formation, contraction of the esophagus and perforation with resulting mediastinitis.

Pack [91] discusses the rotating method of irradiation and cites the results obtained by J. Nielsen (Clinical Results with Rotation Therapy in Cancer of the Esophagus, *Acta Radiol.* **26:** 361, 1945). Of 140 patients, 96 received more than 4,000 r, directed to the cancer. Complete or nearly complete relief from symptoms was obtained immediately in four fifths of the entire group. Death was due to metastases and cachexia, but the majority of patients were able to swallow until the fatal day.

DIAPHRAGMATIC HERNIA

General Observations.—In most instances, the stomach gains access to the thoracic cage through the esophageal opening in the diaphragm.[92] The variable symptoms may simulate those of gastrointestinal, cardiac, respiratory or gallbladder disease; frequently there are no symptoms. Esophagoscopy with roentgenologic examination is the only means of diagnosis. Conservative treatment suffices in the majority of cases, although surgical intervention may become necessary. General discussions of this entity are presented by Bloom,[93] Swan,[94] Stalker and Moskowitz,[95] Shanks [96] and Gilbert.[97]

Roentgenologic Diagnosis.—Kirklin and Hodgson [98] state that search for diaphragmatic hernia should be part of every gastrointestinal examination; the roentgenologic features of the various types of hernia are described in considerable detail. Quénu [99] states that the majority can be diagnosed with a simple roentgenogram of the chest.

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91. Pack, G. T.: Introduction to Symposium on Cancer of the Esophagus and Gastric Cardia, Surgery **23**:867, 1948.

92. Putney, F. J.: Thoracic Stomach Produced by Esophageal Hiatus Hernia and Congenital Short Esophagus, Ann. Int. Med. **28**:1094, 1948.

93. Bloom, J.: Hiatus Hernia, Canad. M. A. J. **57**:9, 1947.

94. Swan, H.: Congenital Diaphragmatic Hernia Through the Pleuroperitoneal Canal, Rocky Mountain M. J. **45**:480, 1948.

95. Stalker, L. K., and Moskowitz, M. J.: New York State J. Med. **48**:641, 1948.

96. Shanks, S. C.: Hiatus Hernia, Brit. J. Radiol. **21**:55, 1948.

97. Gilbert, N. C.: Recurrent Esophageal Hiatus Hernia, M. Clin. North America **32**:213, 1948.

98. Kirklin, B. R., and Hodgson, J. R.: Roentgenologic Characteristics of Diaphragmatic Hernia, Am. J. Roentgenol. **58**:77, 1947.

99. Quénu, J.: Dépistage des hernies diaphragmatiques, Presse méd. **55**:642, 1947.

Unusual Cases.—An unusual case of congenital pleuroperitoneal hiatal hernia in a woman of 25 is described.[100] The position of the kidney below the diaphragm indicated partial formation of the posterior portion of the diaphragm and also that the hernia was of the pleuroperitoneal hiatal type. In a male infant 8 weeks old,[101] examination revealed a congenital defect in the left side of the diaphragm and the presence of the colon in the thoracic cavity. Volvulus of the stomach occurred, followed with a return of the colon to the abdominal cavity, ascent of the stomach to the thoracic cage and death. Interesting congenital diaphragmatic hernias are described in other infants.[102]

Six cases of displacement of the stomach to the right side of the thorax are reported in adults.[103] Only 3 patients had mild symptoms; in all 6, the disorder was suspected on routine roentgenologic examination of the chest. The characteristic finding was a rounded shadow in the right lower portion of the chest, with or without shadows due to gas, and an absence of the gastric gas bubble below the left side of the diaphragm.

Muller [104] concludes that the association of hiatus hernia, diverticula of the colon and gallstones is more common than has been realized; 3 such cases are reported.

Traumatic Diaphragmatic Hernia.—Bollansee [105] reviews traumatic diaphragmatic herniation in detail. Gjellum and others [106] report the case of a man who recovered from a stab wound in the left side of the chest; five months later, while sawing wood, he experienced sudden pain in the left side of the chest and died. Autopsy revealed herniation of the stomach through an old laceration of the diaphragm; the herniated portion of the stomach was gangrenous.

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100. McVicker, J. H., and Harrington, S. W.: Pleuroperitoneal Hiatal Hernia: Report of a Case, Proc. Staff Meet., Mayo Clin. **23**:275, 1948.

101. Owen-Lloyd, E., and Roberts, D.: Congenital Defect of Left Diaphragm with Volvulus of Stomach and Transposition of Viscera, Brit. M. J. **2**:485, 1947.

102. Cassinelli, J. F., and Tiscornia, R. E.: Hernia diafragmática congénita anterior y derecha en un lactante (hernia del hiato de Morgagni, hernia subcosto-esternal de Harrington), Arch. de pediat. d. Uruguay **18**:376, 1947. Thorek, P.: Congenital Diaphragmatic Hernia: Anatomic and Surgical Importance of Left Triangular Ligament of Liver, Arch. Surg. **56**:238 (Feb.) 1948.

103. Teplick, J. G., and Macht, S. H.: Right Sided Thoracic Stomach, Am. J. Roentgenol. **58**:196, 1947.

104. Muller, C. J. B.: Hiatus Hernia, Diverticula and Gallstones: Saint's Triad, South African M. J. **22**:376, 1948.

105. Bollansee, A.: Contribution à l'étude de la hernie diaphragmatique traumatique, Acta clin. belg. **2**:17, 1947.

106. Gjellum, A. B.; Anderson, V. V., and Vickers, C. W.: Diaphragmatic Hernia—a Rare Type, Rocky Mountain M. J. **44**:534, 1947.

A case of traumatic diaphragmatic hernia is reported in a youth of 19.[107] Candolin [108] reports that of 8 cases, diaphragmatic hernia was the result of perforating trauma in 4 and of blunt trauma in 1; 1 was a hiatus hernia, and 2 were congenital. The author recommends surgical treatment during a symptom-free interval. Five patients were operated on through the abdomen, with 2 deaths; 1, through the thorax, with death; 2 were not operated on, and 1 died of incarceration of the stomach.

An analysis of 28 cases of traumatic diaphragmatic hernia is presented by Hughes and his associates.[109] Roentgenographic studies were diagnostic when hollow viscera were involved. When the liver or the omentum was the herniating structure diagnosis was made only at thoracotomy. Sixteen hernias were due to war wounds of the diaphragm, and 9 resulted from automobile accidents, 2 from falls and 1 from a stab wound. Transthoracic repair of the hernia was performed in all cases; in 1, immediate postoperative recurrence necessitated a second operation.

Symptoms.—Stapleton [110] states that he considers hiatus hernia to be a relatively common cause of gastrointestinal complaints. Patients with large hernias and severe symptoms should be operated on if they are in good general condition. During a period of ten months, 24 instances of esophageal hiatus hernia were found in 522 persons whose esophagus and stomach were examined, an incidence of 4.6 per cent.

Radloff and King,[111] in a study of 50 cases, concluded that in only 30 per cent were the symptoms attributable to the hernia; in the majority, concomitant disease seemed to account for the symptoms. Correction of the coexisting disease, reduction of weight and treatment of the underlying emotional factors afforded relief in most cases. Surgery was necessary in only 3. These observations coincide with the experience of the reviewers.

Dack and others [112] state the opinion that a hiatus hernia may act as the trigger mechanism precipitating angina pectoris when the coronary arteries are sclerotic. Pain in the chest due to simple hernia seldom is related to physical effort or to emotional stress. Herniation may produce bleeding, and, when the anemia is severe or leads to vascular

107. Vin Zant, L. E., and Hibbard, J. S.: Traumatic Diaphragmatic Hernia, J. Kansas M. Soc. **48**:504, 1947.

108. Candolin, Y.: On Diaphragmatic Hernia, Acta chir. Scandinav. **95**:61, 1947.

109. Hughes, F.; Kay, E. G.; Meade, R. H., Jr.; Hudson, T. R., and Johnson, J.: Traumatic Diaphragmatic Hernia, J. Thoracic Surg. **17**:99, 1948.

110. Stapleton, J. G.: Oesophageal Hiatus Hernia, Canad. M. A. J. **57**:13, 1947.

111. Radloff, F. F., and King, R. L.: Esophageal Hiatus Hernia, Gastroenterology **9**:247, 1947.

112. Dack, S.; Stone, J.; Grishman, A., and Martin, A. M.: Differential Diagnosis of Diaphragmatic Hernia and Coronary Heart Disease, Bull. New York Acad. Med. **24**:396, 1948.

collapse or shock and the vessels are sclerotic, acute coronary insufficiency may be precipitated. In 50 patients between the ages of 40 and 60 with diaphragmatic hernia, one fourth reported gastrointestinal symptoms alone; a few manifested only cardiovascular symptoms. Almost three fourths of the group experienced "dyspepsia" and dysphagia, with pain in the chest, palpitation of the heart and rapid cardiac rate.

Linn,[113] describing 3 cases of hiatus hernia in which the original diagnosis was angina pectoris, concludes that the sensation of pain arising in a hiatus hernia probably is transmitted over the phrenic nerve or the nerves of the lower part of the thorax. In a case of peritoneopericardial diaphragmatic hernia described by Wilson and Rumel,[114] the symptoms consisted of dyspnea and cyanosis after meals, relieved by vomiting. Roentgenologic examination demonstrated a sharply defined area of opacity in the thorax and the presence of coils of intestine within the pericardium. Repair was followed with the development of peritoneopleural hernia.

Secondary normocytic or hypochromic anemia was present in 11 of 41 patients with hiatus hernia; 4 of the anemic patients gave a history of hematemesis or melena.[115] Hypochromic anemia was corrected by iron therapy in the case of a man whose stools showed no blood but whose roentgenograms revealed a diaphragmatic hernia; no other abnormality was present.[116]

Treatment.—Branwood [117] recommends reduction in weight, a bland diet and administration of antacids and antispasmodic drugs; surgical treatment is rarely required.

Olsen and Harrington [118] present a special consideration of 220 cases of short esophagus and partial thoracic stomach. Dysphagia occurred in 165 cases, substernal distress in 71, esophageal pain in 20 and hemorrhage in 18; there were no esophageal symptoms in 17. Stricture of the lower part of the esophagus was present in 30; a carcinoma was associ-

113. Linn, G. C.: Hiatus Hernia Confused with Coronary Thrombosis, New York State J. Med. **48**:303, 1948.

114. Wilson, A. K., and Rumel, W. R.: Peritoneopericardial Diaphragmatic Hernia: Report of a Case, Am. J. Roentgenol. **57**:42, 1947.

115. Ritchey, J. O., and Winsauer, H. J.: Anemia and Its Relation to Diaphragmatic Hernia, Am. J. M. Sc. **214**:476, 1947.

116. Cohen, A.; Dorfman, W., and Epstein, S.: Severe Anemia in a Case of Diaphragmatic Hernia, New York State J. Med. **48**:90, 1948.

117. Branwood, A. W.: Esophageal Hiatus Hernia, Edinburgh M. J. **55**:50, 1948.

118. Olsen, A. M., and Harrington, S. W.: Esophageal Hiatal Hernias of the Short Esophagus Type: Etiologic and Therapeutic Considerations, J. Thoracic Surg. **17**:189, 1948.

ated with the hernia in 3. Dilations of associated strictures were carried out in 145 of the 220 cases, with generally satisfactory results. Interruption of the phrenic nerve was performed alone in 4 and together with surgical repair in 17. The prognosis for surgical treatment of this type of hernia is not considered favorable. Shortening is attributed to peptic ulceration of the esophagus; the latter may be a consequence of excessive or prolonged vomiting or of physiologic incompetence of the sphincter at the cardia.

In an excellent paper, which should be read in its entirety, Harrington [119] describes the surgical treatment of various types of diaphragmatic hernia. In a series of 430 cases there were 17 operative deaths, a mortality rate of 4.0 per cent. Recurrences were noted in 10 cases, of which 9 were of esophageal hiatus hernia and 1, of congenital diaphragmatic hernia.

According to Soutter,[120] diaphragmatic hernia may be satisfactorily repaired with a low mortality rate: It was 0 in 37 cases in which the thoracic approach was used, and 4 per cent in 25 cases in which the abdominal approach was used. Though recurrence is frequent, symptomatic relief occurs in a much higher percentage of cases. Surgical treatment is indicated in patients suffering from pain, vomiting, obstruction, anemia or angina. The supradiaphragmatic approach [121] is considered simple and easy; there were fewer postoperative complications and recurrences when this method was used. There were no deaths in 51 cases in which operation was performed; postoperative complications were observed in 5.

THE STOMACH

Gastric Secretion.—Davenport [122] studied the oxidative metabolism of the forestomach and stomach of the mouse and noted a high rate of oxygen uptake, unaffected by the addition of substrates and inhibited in differing degrees by cyanide, iodoacetate, fluoride and arsenite. The oxygen uptake was increased significantly by histamine but was unaffected by enterogastrone, urogastrone, carbaminoylcholine (doryl®) and thiocyanate. The stomach produced and oxidized lactic and pyruvic acid; it reduced pyruvic acid to lactic acid in the presence or absence

119. Harrington, S. W.: Various Types of Diaphragmatic Hernia Treated Surgically, Surg., Gynec. & Obst. **86**:735, 1948.

120. Soutter, L.: An Analysis of the Cases of Hiatus Hernia Treated by Surgery at the Massachusetts General Hospital, S. Clin. North America **27**:1121, 1947.

121. Sweet, R. H.: The Repair of Hiatus Hernia of the Diaphragm by the Supradiaphragmatic Approach, New England J. Med. **238**:649, 1948.

122. Davenport, H. W.: Oxidative Metabolism of the Mouse Stomach, Gastroenterology **9**:293, 1947.

of pyruvic acid oxidation. Conway and Brady [123] discuss the mechanism of hydrochloric acid formation with particular reference to the role of carbonic acid and organic acids (e. g., phosphopyruvic acid).

With the use of indicator dyes in isolated gastric mucosa from frogs and polecats, Bradford and Davies [124] found the site of formation of acid to be at or near the wall of the canaliculi of the delomorphous cells.

Teorell [125] states that the variations of concentration of electrolytes in the mammalian gastric juice are the result of the diffusion of electrolytes across the mucosa, which acts as a "dialyzing membrane." A theory of interdiffusion of two binary electrolytes is presented as the basis for a model of the stomach-blood system. The most important consequences of the work were that variations of acidity and base and total concentration of chlorides were found to be functions of the rate of secretion only, and that the acidity and the total concentration of chlorides increased with the rate of secretion, where the concentration of base varied inversely as the rate of secretion.

In a continuation of experiments to determine whether the production of electrical energy by the stomach plays a role in the formation of hydrochloric acid, Hokin and Rehm [126] found that the decrease in the potential difference across the stomach when 0.9 per cent saline solution, in contact with the mucosa, was replaced by a relatively dilute saline solution was due primarily to an increase in diffusion potential and not to a change in the electrical characteristics of the stomach. No significant change in the rate of acid secretion was noted.

Davies and his co-workers,[127] in a highly interesting group of papers, report on the mechanism of secretion of hydrochloric acid. Experiments were performed on the isolated gastric mucosa of the frog and toad. The results support the view that the reaction fundamentally concerned is

123. Conway, E. J., and Brady, T.: Mechanism of High Acid Production by Yeast and Its Bearing on Hydrochloric Acid Formation in the Stomach, Nature, London **159**:137, 1947.

124. Bradford, N. M., and Davies, R. E.: The Site of Formation of Gastric HCl as Determined by Indicators, Biochem. J. **42**:XII, 1948.

125. Teorell, T.: Electrolyte Diffusion in Relation to the Acidity Regulation of the Gastric Juice, Gastroenterology **9**:425, 1947.

126. Hokin, L. E., and Rehm, W. S.: Effect of Dilute Saline Solutions on the Gastric Potential and the Secretion of HCl, Am. J. Physiol. **151**:380, 1947.

127. (*a*) Davies, R. E.; Longmuir, N. M., and Crane, E. E.: Elaboration of Hydrochloric Acid by Gastric Mucosa, Nature, London **159**:468, 1947. (*b*) Davies, R. E., and Terner, C.: Secretion of Water by Isolated Gastric Mucosa, Biochem. J. **42**:XIII, 1948. (*c*) Davies, R.: Hydrochloric Acid Production by Isolated Gastric Mucosa, ibid. **42**:609, 1948. (*d*) Davies, R., and Longmuir, N. M.: Production of Ulcers in Isolated Frog Gastric Mucosa, ibid. **42**:621, 1948.

expressed in the formula $H_2O \rightarrow H^+ + OH^-$. The hydrogen ions are elaborated by means of energy available from the metabolism of glucose. The H^+ ions are secreted, and the OH^- ions are finally neutralized by carbon dioxide and passed into the blood or nutrient medium. This process is comparable with Hollander's theory of membrane hydrolysis and explains the increase in carbon dioxide which occurs during secretion of acid. In further studies, Davies and Longmuir [127d] found that in the absence of external supplies of carbon dioxide (normally required to neutralize the alkali formed concomitantly with the acid), ulceration and perforation occurred in tied bags of frog gastric mucosa, provided the rate of acid secretion was high; tied mucosa with low rates of secretion showed little or no ulceration. It is suggested that the ideal antacid for the prevention of ulceration should evolve carbon dioxide in the presence of acid and should contain cations which do not upset the acid-base balance of the blood.

The reabsorptive and secretory activity of the stomach of the salamander was studied under ultraviolet light by means of luminescent vital dyes, biologically positive uranin and biologically negative acriflavine N. F. (trypaflavine®).[128] The experiments are interpreted as demonstrating that "the parietal cells, particularly during secretion, behave as negative centers which draw sodium into the blood and acidify the stomach content in this manner. Also, that in the opposite direction, basic dyes of the trypaflavine type travel from the blood into the stomach." According to the authors, the decomposition of sodium chloride near the gastric mucosa should be considered a process of electrolysis, since the positive half of the salt travels as a molecule rather than as an ion.

Kurtz and Clark [129] present experimental data obtained on 4 dogs, which demonstrate an inverse relation between the amount of hydrochloric acid secreted by the stomach and the quantity of carbon dioxide diffusing into the gastric lumen when secretion is simulated by histamine. The relation is interpreted to indicate that secretion of acid is accompanied by a proportional decrease in the carbon dioxide tension in the gastric tissues and blood. The authors state the belief that these findings support the view that carbon dioxide is utilized in some way in the formation of hydrochloric acid, and that the carbonic anhydrase contained in the parietal cell is a functional part of this mechanism.

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128. Keller, R., and Pisha, B. V.: Electrolysis in the Stomach, Rev. Gastroenterol. **14**:495, 1947.

129. Kurtz, L. D., and Clark, B. B.: The Inverse Relationship of the Secretion of Hydrochloric Acid to the Tension of Carbon Dioxide in the Stomach, Gastroenterol. **9**:594, 1947.

Lambling and Gosset [130] question the theory, propounded by Boldyreff, that the alkaline secretions of the small intestine regurgitate to the stomach in a physiologic way to neutralize the acidity of the gastric secretion. Studies of dogs indicated to Pincus and others [131] that pancreatic juice provides buffering material which serves to neutralize acid gastric content. No correlation was evident between the acidity of the duodenal content and the volume of pancreatic secretion.

Horstmann [132] states that the acid component of gastric juice, which is supposed to be a solution of pure hydrochloric acid, was computed to have an acidity and a chloride concentration of approximately 180 milliequivalents per liter, whereas the chloride of the nonacid component was approximately 70 to 80 milliequivalents per liter. The nonacid secretion, says the author, probably possesses an alkalinity of approximately 35 milliequivalents per liter.

Grossman and others [133] report that distention of the pyloric portion of the stomach stimulates the secretion of hydrochloric acid by the fundic glands in dogs. The effect occurs when all nervous connections between the stimulated and responding portions of stomach are interrupted and thus demonstrates the existence of a hormone for gastric secretion.

A colorimetric method for the detection of histamine is described [134]; it is adapted for the determination of free and conjugated histamine in animal tissues and body fluids. In another study,[135] gastric juice secreted in response to histamine and to insulin usually contained histamine. Juice secreted in response to mecholyl chloride uniformly contained readily estimable quantities of histamine. Three fourths of samples of gastric juice from Pavlov pouches after a meat meal contained detectable amounts of histamine. In general, high concentrations of histamine activity were present in juice in which the concentration of hydrochloric acid was comparatively low; high concentrations of acid in the juice, as a rule, were associated with low concentrations of histamine activity.

130. Lambling, A., and Gosset, J. R.: Le reflux des sécrétions alcalines duodéno-pancréatico-biliares en physio-pathologie gastrique: (*a*) I. Etude critique, clinique et expérimentale de la théorie de Boldyreff, Arch. d. mal. de l'app. digestif **36**:529, 1947; (*b*) II. La physio-pathologie du reflux (hypochlorhydrie et anachlorhydrie par reflux), ibid. **37**:165, 1948.

131. Pincus, I. J.; Thomas, J. E.; Hausman, D., and Lachman, P. O.: Relationship Between the p_H of the Duodenal Content and Pancreatic Secretion, Proc. Soc. Exper. Biol. & Med. **67**:497, 1948.

132. Horstmann, P.: Contribution to the Understanding of the Gastric Acidity, Acta physiol. Scandinav. **14**:27, 1947.

133. Grossman, M. I.; Robertson, C. R., and Ivy, A. C.: Proof of a Hormonal Mechanism for Gastric Secretion—the Humoral Transmission of the Distention Stimulus, Am. J. Physiol. **153**:1, 1948.

134. Rosenthal, S. M., and Tabor, H.: An Improved Colorimetric Method for the Estimation of Histamine, J. Pharmacol. & Exper. Therap. **92**:425, 1948.

135. Code, C. F.; Hallenbeck, G. A., and Gregory, R. A.: Histamine Content of Canine Gastric Juice, Am. J. Physiol. **151**:593, 1947.

Obrink,[136] on the basis of experiments on dogs with vagotomized gastric pouches and on cats given histamine, suggests that there is no threshold value for the action of histamine in stimulating gastric secretion. The regulation of acidity was due mainly to processes of diffusion. A simple relation was noted between the rate of secretion and the total output of hydrochloric acid. Enterogastrone exerted a depressing influence on the rate of secretion, but no specific effect on the acidity or concentration of chloride.

Hanson, Grossman and Ivy[137] report that the doses of histamine which produced minimal and maximal amounts of gastric secretion in dogs were established, and that threshold values were obtained for human beings. Minimal and maximal doses, whether given subcutaneously or intravenously, were similar for intact and vagotomized dogs with total pouches, indicating that vagotomy does not alter the response of gastric secretion to histamine in the dog and that histamine is not inactivated during absorption from subcutaneous tissues. The maximal secretory response to histamine in intact and in vagotomized dogs was similar and amounted to an average of 80 cc. per hour, with a total acid concentration of 140 milliequivalents per liter. Human subjects are more sensitive to histamine than dogs; acid responses were obtained with a dose averaging about one tenth the minimal dose in the dog. The parietal cell seems to be the most sensitive in the body to histamine, although it is possible that this sensitivity may be equaled at times by that of the cerebral vessels. The characteristics of the gastric response to histamine, the possible mode of action and the evidence bearing on the role of histamine as a physiologic stimulant of gastric secretion are discussed.

Ihre[138] found that the standard error in the computation of volume of aspirated juice was less when a double lumen tube was employed and both gastric and duodenal contents were aspirated. The reliability of the histamine test was increased when continuous suction was maintained.

A preparation of histaminase extracted from the renal cortex of hogs inhibited the response of the gastric secretion to histamine in dogs.[139]

Extracts of the urine were obtained from dogs subjected to the removal of various endocrine glands, and the effect of the extracts on

136. Obrink, K. J.: Studies on the Kinetics of the Parietal Secretion of the Stomach, Acta physiol. Scandinav. (supp. 51) **15**:1, 1948.

137. Hanson, M. E.; Grossman, M. I., and Ivy, A. C.: Doses of Histamine Producing Minimal and Maximal Gastric Secretory Responses in Dog and Man, Am. J. Physiol. **153**:242, 1948.

138. Ihre, B. J. E.: Studies in Gastric Secretion with an Improved Histamine Test, Acta med. Scandinav., 1947, supp. 196, p. 322.

139. Grossman, M. I., and Robertson, C. R.: Inhibition by Histaminase of Gastric Secretion in Dogs, Am. J. Physiol. **153**:477, 1948.

histamine-stimulated gastric secretion was studied.[140] Thyroidectomy plus oophorectomy did not alter greatly the inhibitory effect of the extract. Hypophysectomized dogs did not produce the inhibiting substance in amounts adequate to diminish gastric secretion.

Ethyl-3, 3-dimethylallyl barbituric acid proved to be a very powerful stimulant to gastric secretion in dogs with gastric fistulas.[141] Vagotomy, anesthesia and tetraethylammonium chloride prevented its action. The level of blood sugar remained normal, indicating that the stimulant had a mode of action different from that of insulin. The authors conclude that its effect is on the central nervous system, probably in the hypothalamus.

A definite increase in the acid content of the stomach occurred during the periods of hypoglycemia in 5 patients with schizophrenia treated by insulin shock.[142] Reed,[143] using an Ewald test meal, observed either anacidity or "subacidity" prior to prefrontal lobotomy in 9 patients; all patients manifested increased acidity after lobotomy. The findings suggested the possibility that there is depression of gastric secretion with the depression of mental reaction and that with the restoration of some normal mental function the gastric secretion is increased. Further observations on the subject would be of interest.

Methyl scopolamine is a potent inhibitor of gastric secretion in the dog; both scopolamine and atropine are slightly less effective.[144] Enterogastrone does not inhibit the histamine-stimulated gastric secretion of the anesthetized cat.[145] In 14 human subjects, pyribenzamine® (N′-pyridyl-N¹-benzyl-N-dimethyl-ethylene diamine hydrochloride) in a dosage of 50 mg. twice daily up to 100 mg. four times daily, usually failed to prevent the increase in gastric acidity induced by histamine.[146]

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140. Kaulbersz, J.; Patterson, T. L.; Sandweiss, D. J., and Saltzstein, H. C.: Alterations in Urogastrone Excretion Produced by Extirpation of Various Endocrine Glands, Am. J. Physiol. **150**:373, 1947.

141. Ballem, C. M.; Noble, R. L., and Webster, D. R.: New Parasympathetic Stimulant—Ethyl 3:3 Dimethylallyl Barbituric Acid, Canad. M. A. J. **58**:447, 1948.

142. Hiles, C. H.: Gastric Secretory Response in Hypoglycemia as Produced During Insulin Shock Therapy, Am. J. M. Sc. **214**:667, 1947.

143. Reed, J. A.: A Study of Gastric Acids in Prefrontal Lobotomy, Gastroenterology **10**:118, 1948.

144. Strom, G., and Uvnäs, B.: The Effect of Atropine, Scopolamine and Some Related Synthetic Drugs on the Insulin-Induced Gastric Secretion of the Dog, Acta physiol. Scandinav. **15**:6, 1948.

145. Uvnäs, B.: The Effect of Enterogastrone on the Gastric Secretion of the Cat Stimulated by Continuous Administration of Histamine, Acta physiol. Scandinav. **15**:1, 1948.

146. Perry, E. L., and Horton, B. T.: Use of Pyribenzamine in Prevention of Histamine-Induced Gastric Acidity and Headache and in Treatment of Hypersensitiveness to Cold, Am. J. M. Sc. **214**:553, 1947.

Acetylsalicylic acid in doses of 70 to 95 mg. per kilogram did not stimulate gastric secretion in a dog with a Cope pouch; however, doses of twice that amount increased the volume and the production of acid.[147] The data suggest that an increase in secretion does not occur unless the dose is sufficient to induce gastrointestinal symptoms.

Ten experiments were conducted on 5 patients subjected to fever therapy in a cabinet for three-fourths to three hours.[148] Peak body temperatures were maintained at levels ranging from 102 to 105.7 F. (38.9 to 40.9 C.); complete anacidity developed in only 2 instances. Six similar experiments were performed on 4 patients in whom peak body temperatures of 103.6 to 106.1 F. (39.8 to 41.2 C.) were maintained for three and one-half to five and one-half hours; complete anacidity developed in every one. The difference is ascribed to the degree and duration of the induced fever. The duration of the anacidity varied considerably. Short wave diathermy over the stomach produced no demonstrable effect on production of free or total acid in 10 normal fasting human subjects.[149]

Hofstetter [150] noted a discrepancy between the p_H of gastric content as estimated in vitro and that determined by intragastric measurement using the electrode method.

Oberhelman and Dragstedt [151] found that the secretory response to a standard dose of histamine in dogs with a totally isolated gastric pouch was greatly reduced by bilateral vagotomy. Atropine (2 mg. subcutaneously) similarly reduced the response to histamine. In 15 patients with peptic ulcer treated by transthoracic section of the vagus nerves and in 18 patients with ulcer who underwent transabdominal gastric vagotomy, the response to a standard dose of histamine likewise was reported as greatly reduced. In dogs with total gastric pouches, section of the vagus nerves above the diaphragm reduced the volume of the twenty-four hour gastric secretion by 56 per cent and the total output of hydrochloric acid by 77 per cent.[152] Vagotomy reduced the peptic power of the twenty-four hour secretion in 7 of 8 animals. After complete vagotomy, the response to a standard dose of histamine was considerably reduced.

147. Clark, B. B., and Adams, W. L.: The Effect of Acetylsalicylic Acid on Gastric Secretion, Gastroenterology **9**:461, 1947.

148. Bandes, J.; Hollander, F., and Bierman, W.: The Effect of Physically Induced Pyrexia on Gastric Acidity, Gastroenterology **10**:697, 1948.

149. Palmer, E. D.: The Effect of Short Wave Diathermy on the Secretory Activity of the Fasting Normal Human Stomach, Am. J. Digest. Dis. **14**:342, 1947.

150. Hofstetter, F.: p_H-Messungen mit der Glaselektrode im Magensaft, Gastroenterologia **72**:201, 1947.

151. Oberhelman, H. A., Jr., and Dragstedt, L. R.: Effect of Vagotomy on Gastric Secretory Response to Histamine, Proc. Soc. Exper. Biol. & Med. **67**:336, 1948.

152. Woodward, E. R.; Dragstedt, L. R.; Tovee, E. B.; Oberhelman, H. A., Jr., and Neal, W. B., Jr.: A Quantitative Study of the Effect of Vagotomy on Gastric Secretion in the Dog, Proc. Soc. Exper. Biol. & Med. **67**:350, 1948.

Trethewie,[153] using a test meal, noted achlorhydria in 2 of 12 patients shortly after the development of dermal hypersensitivity to mustard applied to the skin.

Fourteen Polish prisoners of war, fed a diet poor in protein and thiamine, manifested a progressive decrease in the level of hydrochloric acid produced over a period of three years. After their liberation, and without change in their locale or diet, the output of acid returned to normal levels.[154] The incidence of achylia gastrica, as determined by test meals given at the University of Warburg, Germany, rose from 5.6 per cent in 1939 to 21.7 per cent in 1945.[155]

Gastric Mucus.—Glass and Boyd[156] describe a new quantitative colorimetric method for the measurement of the total dissolved mucin. The procedure involves double fractionation of the centrifuged gastric juice with trichloracetic acid and acetone and the colorimetric reaction between gastric mucin and the Folin-Ciocalteau reagent, containing phosphotungstic-phosphomolybdic acid.

Ninety-nine experiments on dogs with Heidenhain pouches[157] were performed to test the effect of eugenol (4-allyl-2-methoxy-phenol), a derivative of clove oil, on the secretion of gastric mucus. A 5 per cent emulsion yielded large volumes of mucus with a high p_H. A method is described for the permanent metachromatic staining of mucus in sections of tissue and in smears.[158] The principal stain is 0.25 per cent toluidine blue O, dissolved in 0.25 per cent borax solution. Preservation is accomplished by twice covering the slide with a 0.5 per cent solution of potassium bichromate saturated with mercuric chloride.

Wolf and Wolf[159] tested the local action of twenty-five different drugs on the gastric mucosa of a human subject with a gastric fistula.

153. Trethewie, E. R.: Mustard Hypersensitivity and Achlorhydria, M. J. Australia **34**:633, 1947.

154. Komalewski, K.: Étude de l'acidite gastrique chez des prisonniers de guérre presentant differents troubles gastrointestinaux, Acta gastroenterol. belg. **10**:503, 1947.

155. Bottner, H.: Achylia Gastrica in Recent Years, Med. Klin. **42**:104, 1947.

156. Glass, G. B., and Boyd, L. J.: (*a*) Studies on Dissolved Mucin (Muco-protein) of the Gastric Juice: I. Preliminary Tests and the Rationale for a New Colorimetric Quantitative Method for the Determination of Dissolved Gastric Mucin, Rev. Gastroenterol. **15**:396, 1948; (*b*) II. A New Quantitative Colorimetric Method for the Determination of Total Dissolved Gastric Mucin, ibid. **15**:511, 1948.

157. (*a*) Hollander, F., and Lauber, F. U.: Eugenol as a Stimulus for Gastric Mucous Secretion, Proc. Soc. Exper. Biol. & Med. **67**:34, 1948. (*b*) Hollander, F.; Lauber, F. U., and Stein, J. J.: p_H of Gastric Mucous Secretion, Am. J. Physiol. **152**:645, 1948.

158. Hess, M., and Hollander, F.: Permanent Metachromatic Staining of Mucus in Tissue Sections and Smears, J. Lab. & Clin. Med. **32**:905, 1947.

159. Wolf, S., and Wolf, H. G.: Studies on Mucus in the Human Stomach: Estimation of Its Protective Action Against Corrosive Chemicals Applied to the Gastric Mucosa and Attempts at Quantitation of Gastric Mucin by Two Chemical Methods, Gastroenterology **10**:251, 1948.

Direct observation was supplemented by microscopic study of scrapings from the membrane. The gastric mucosa was found to be more resistant to the action of irritants than was the skin of the forearm, a reaction attributable in great part to the protective action of mucus. Two separate methods for the titration of mucin yielded more or less parallel results. The measurement of the content of mucin in gastric juice did not necessarily reflect the quantity of mucus produced, since the highly tenacious substance may adhere to the mucosa and not appear in a specimen withdrawn through a tube. A dissociation between the production of mucin and the concentration of acid was found under certain circumstances.

Uropepsin.—In 3 cats surviving total gastroectomy for fourteen, sixty-four and one hundred and forty-four days, respectively, uropepsin disappeared completely from the urine two to six days after operation.[160] There was no evidence of return of uropepsin in 1 cat which survived for twenty weeks and which had regained its preoperative weight. The character of the diet and the appetite are more important factors in altering uropepsin output in cats than the administration of caffeine and histamine.[161] Uropepsin was found in the urine of normal rats in amounts varying from 2.7 to 19.0 mg. in twenty-four hours (expressed in milligrams of tyrosine liberated from a hemoglobin substrate by the total output of urine in twenty-four hours). In most instances, uropepsin disappeared from the urine within twenty-four hours after total gastrectomy.[162] These observations on uropepsin are of considerable interest and warrant further study.

Urease.—Urease is found in the fundic mucosa of the human stomach [163]; it is present in the gastric juice in amounts inversely proportional to the degree of acidity; it is destroyed by pepsin and hydrochloric acid.

Peptic Activity.—A method for determination of peptic activity, using a substrate of dried plasma or serum protein, is described.[164]

Bacteriologic Examination.—Bacteriologic studies were made on the gastric juice of 106 patients in Puerto Rico.[165] In each instance, a

160. Bucher, G. R., and Ivy, A. C.: Disappearance of Uropepsin from the Urine of Gastrectomized Cats, Am. J. Physiol. **150**:415, 1947.

161. Bucher, G. R., and Anderson, A.: Uropepsin Output in Cats Treated with Caffeine and Histamine, Am. J. Physiol. **153**:454, 1948.

162. Balfour, D. C.; Preston, F. W., and Bollman, J. L.: The Disappearance of Uropepsin Following Total Gastrectomy, Gastroenterology **10**:880, 1948.

163. Hollan, S.: Gastric Urease, Brit. J. Exper. Path. **28**:365, 1947.

164. Hunt, J. M.: A Method for Estimating Peptic Activity in Gastric Contents, Biochem. J. **42**:104, 1948.

165. Morales, F. H., and Baralt, J.: Note on Bacteriologic Examination of Stomach Contents in Puerto Rico, Puerto Rico J. Pub. Health & Trop. Med. **23**:444, 1948.

sterile gastric tube was introduced by mouth and the gastric residue aspirated with a sterile syringe. The residue and the material aspirated sixty minutes after the administration of histamine hydrochloride were examined immediately and cultured without previous neutralization in 3 per cent blood agar, bile salt (MacConkey) agar, and tryptose phosphate and thioglycolate broths. In the residue, gram-positive and gram-negative cocci appeared with great frequency, the gram-positive cocci slightly predominating. In the histamine-stimulated content, gram-negative bacteria predominated. In type and frequency the organisms encountered corresponded, in general, to those present in the throats of normal Puerto Ricans.

Gastric Motility and Emptying.—Ginsberg, Feldman and Necheles [166] found that fear was a factor in suppressing gastric motility and tone in the dog when obnoxious odors were perceived. In man, appetite and the desire to eat may disappear with exposure to certain odors, but gastric motility and tone need not be affected. Appetite and the desire to eat appear to be primarily psychic phenomena.

D-amphetamine sulfate produced a transient depression or abolition of gastric hunger contractions in intact dogs, when administered subcutaneously; however, that symptom was not the sole or the most important factor in the depression of food intake, for food intake was still reduced after recovery of the gastric contractions.[167] Doses too small to depress gastric motor activity depressed food intake. Dogs with vagotomized total pouches manifested depressed food intake, although d-amphetamine sulfate did not inhibit gastric contractions. Attention is directed to the importance of the central nervous system in hunger and appetite and to the secondary role of gastric hunger contractions.

Serial roentgenograms of dogs' stomachs were made after marking the curvatures with lead shot and the muscularis mucosae with colloidal thorium dioxide (thorotrast®) in the submucosa; the evidence is interpreted as demonstrating that movement of the gastric mucosa is due to contraction of the muscularis mucosae independent of the muscularis propria.[168]

Thirty normal human subjects were given test meals containing varying amounts of fat.[169] Changes in the volume of the stomach during

166. Ginsberg, R. S.; Feldman, M., and Necheles, H.: Effect of Odors on Appetite, Gastroenterology **10**:281, 1948.

167. Sangster, W.; Grossman, M. I., and Ivy, A. C.: Effect of D-Amphetamine on Gastric Hunger Contractions and Food Intake in the Dog, Am. J. Physiol. **153**:259, 1948.

168. Brooks, F. P.; Stevens, L. W.; Pendergrass, E. P., and Bassols, F.: Experimental Studies on the Motility of the Gastric Mucosa in Dogs, Am. J. Roentgenol. **59**:482, 1948.

169. Annegers, J. H., and Ivy, A. C.: The Effect of Dietary Fat Upon Gastric Evacuation in Normal Subjects, Am. J. Physiol. **150**:461, 1947.

a four-hour period were detected by recording the outline of the stomach, containing a small amount of barium sulfate in suspension, on a roentgenogram. Delayed gastric evacuation, attributable to the fat content of the test meal, was statistically significant. Chloral hydrate, bromisovalum (bromural®) and paraldehyde did not consistently increase the motility of the normal human stomach [170]; consistently increased motility was noted when pentobarbital sodium was given. Tetraethylammonium chloride,[171] given intravenously in doses of 0.3 to 0.5 Gm., rapidly and consistently induced a cessation of gastric and intestinal peristalsis and a pronounced decrease in gastric tone. Distinct delay in gastric emptying, as indicated by films taken three hours after a barium sulfate meal, occurred in 45 per cent of 20 normal human subjects. In a survey made in México, D. F., the emptying time of the stomachs of persons given barium sulfate test meals averaged from five to six hours; there is retardation of emptying time at higher altitudes.[172]

Section of the left phrenic nerve [173] is followed with gastric hypotonia and hypokinesia and with the accumulation of a large gastric gas bubble; gastric emptying time is shortened. Barium sulfate appeared to puddle in a moderately contracted intestine. No symptoms were observed which could be associated with the so-called gastrocardiac reflex. After phrenicotomy and vagotomy, the vomiting and gaseous distention of the gastrointestinal tract which occur with vagotomy alone are absent.

Several substantial meals, eaten at short intervals, progressively lengthen the usual two hour duration of the period of vasodilatation of the skin that follows a single meal.[174]

The Scandinavian workers have not yet escaped from the fallacious concept that all gastric disorders result from disturbances in gastric motility. Such a relation is alleged to have been found in a study of 82 patients with "dyspeptic" symptoms but no ulcer or carcinoma, 36 persons without gastric symptoms, 38 with peptic ulcer and 6 with gastric carcinoma.[175] Increase or lack of peristalsis and tone was considered a

170. Northrup, D. W., and Vauliere, E. J.: The Effect of Central Nervous System Depressants on the Emptying Time of the Human Stomach, J. Pharmacol. & Exper. Therap. **93**:208, 1948.

171. Dodds, D. C.; Ould, C. L., and Dailey, M. E.: The Effect of Tetraethylammonium Chloride on Gastric Motility in Man, Gastroenterology **10**:1007, 1948.

172. Nimeh, W.: Emptying of the Normal Stomach in Altitudes, Rev. Gastroenterol. **15**:763, 1947.

173. Jefferson, N. C., and Necheles, H.: The Effect of Phrenicotomy on Gastrointestinal Mechanisms, Proc. Soc. Exper. Biol. & Med. **68**:166, 1948.

174. Roth, G. M., and Sheard, C.: Maintenance of Vasodilatation of the Extremities of Normal Individuals for a Prolonged Period by the Ingestion of Two to Four Substantial Meals in Close Succession, Am. J. Physiol. **152**:183, 1948.

175. Brummer, P.: On the Significance of Motility Disturbances of the Stomach as a Cause of Gastric Distress, Acta med. Scandinav. **128**:338, 1947.

disturbance of motility. Alterations in motility are stated to be more important than gastric acidity in cases of "gastric symptoms." Similarly, Wegelius,[176] in a combined clinical and roentgenologic study of 37 patients with peptic ulcer, 82 with "dyspeptic" symptoms and 36 persons who served as controls, reached the conclusion that a motor abnormality of some sort can be demonstrated in 90 per cent of patients with "dyspepsia," as compared with only 10 to 15 per cent of healthy persons. Disturbances in motility were noted in 31 of 35 patients with ulcers given roentgen examinations during an attack of pain; of 5 patients examined when pain was absent, none manifested such a disturbance. The latter observations are in distinct contrast to the well controlled investigations of Bonney and Pickering, reviewed in 1948.

Digestion of Protein.—Fetal rats with functioning placentas apparently partially digest milk and starch placed in the stomach.[177] The capacity to digest meat is less well developed or absent. Cytronberg and others[178] speculate on various aspects of the digestion of protein in the stomach on the basis of various physicochemical data.

Diagnosis of Gastric Disease.—Comparative studies in dogs with suspensions of barium sulfate and of tetraiodophthalimidoethanol indicated to Jones and his associates[179] that the iodinated medium more completely and accurately outlined experimentally produced gastric lesions. The insufflation of air into the stomach through a Levin tube, followed with the introduction of barium sulfate, is reported to be helpful in delineating small lesions at the gastroesophageal junction.[180] Rossien[181] reviews the embryologic development and anatomic features of the stomach in relation to the diagnosis of gastric disease.

Distribution of Paricta! Cells.—On the basis of a study of 200 cases in which surgical resection of the stomach was performed for gastric carcinoma or for peptic ulcer of the stomach or the duodenum, Meiss-

176. Wegelius, C.: Pathological Gastric Motility: A Criterion of Roentgen Diagnosis in Cases of Gastric Distress, Acta med. Scandinav. **128**:349, 1947.

177. Hartmann, J. F., and Wells, L. J.: Fate of Food Introduced Directly Into the Fetal Stomach, Proc. Soc. Exper. Biol. & Med. **68**:327, 1948.

178. Cytronberg, S. S.; Leaño A. del Castillo, A., and de Lachica, A.: Study of the Digestive Capacity of the Stomach by Means of Physico-Chemical Methods, Rev. Gastroenterol. **14**:721, 1947.

179. Jones, G. E.; Chalecke, W. E.; Dec, J.; Schilling, J. A.; Ramsey, G. H.; Robertson, H. D., and Strain, W. H.: Iodinated Organic Compounds as Contrast Media for Radiographic Diagnoses: VIII: Studies on Tetraiodophthalimidoethanol as a Medium for Gastro-Intestinal Visualization, Radiology **49**:143, 1947.

180. Latraverse, V.: A Procedure Helping the X-Ray Examinations of the Gastro-Esophageal Segment, Am. J. Digest. Dis. **14**:298, 1947.

181. Rossien, A. X.: Important Embryological and Anatomical Considerations for the Diagnosis of Gastric Disease, Rev. Gastroenterol. **14**:539, 1947.

ner[182] concludes that the number of parietal cells diminishes as the pylorus is approached and is somewhat less along the lesser curvature than in corresponding areas on the walls or the greater curvature. The only quantitative change of significance was that in many cases of carcinoma there was a diminution of the number of parietal cells in the body and the fundus of the stomach, whereas in cases of peptic ulcer (especially duodenal ulcer) such a diminution was less frequent. A reduction in the number of parietal cells was not a constant finding in cancer of the stomach; there was an abundance of parietal cells in many cases of cancer and complete anacidity. None of the stomachs showed complete absence of such cells. As determined with routine stains, there were no qualitative changes in individual parietal cells which could be correlated with ulcer or with cancer.

In an important paper, Meyers[183] describes the microscopic characteristics of the gastric mucosa in 25 cases of duodenal ulcer, 25 of gastric ulcer, 25 of gastric cancer in which free hydrochloric acid was present, 25 in which achlorhydria was present and 25 in which the hematologic findings and clinical symptoms were those of pernicious anemia. Specimens were obtained at the time of gastrectomy or gastric resection. In addition, blocks were taken in 10 cases of pernicious anemia in which specimens were obtained at necropsy. Of particular interest, perhaps, is the fact that the number of parietal cells in the fundus varied in the four conditions: In the cases of duodenal ulcer, the number of parietal cells ranged from 60 to 90 per high power field; there were from none to 40 in those of gastric ulcer, from 25 to 40 in those of gastric cancer with free hydrochloric acid, from none to 10 in those of gastric cancer without hydrochloric acid, and none in those of pernicious anemia. Meyers concludes:

> It does appear that gastritis is the same, in whatever pathologic condition of the upper portion of the gastrointestinal tract it occurs; it begins with an inflammatory reaction accompanied by hyperemia and cellular infiltration; if chronicity is allowed to develop by virtue of persistence of the etiologic factor, the mucous membrane passes through successive stages of glandular destruction, erosion, formation of cysts, destruction of the muscularis mucosae and finally, a state of atrophic anadenia. The glandular elements which still persist make sporadic attempts at regeneration, trying to regain normal function, but finally fail and are replaced by an intestinal type of mucous membrane. The end result is the same, be the associated condition ulcer, cancer or pernicious anemia.

Diverticula.—The subject is reviewed by Chavarri[184] and by Ficarra.[185]

182. Meissner, W. A.: Distribution of Parietal Cells in Gastric Disease, Arch. Path. **44**:261 (Sept.) 1947.

183. Meyers, W. C.: A Study of Gastric Mucosa in Various Diseases Affecting the Upper Part of the Gastrointestinal Tract, Gastroenterology **10**:923, 1948.

184. Chavarri, M. A.: Gastric Diverticulosis, Prensa méd. argent. **34**:1689, 1947.

185. Ficarra, B. J.: Gastric Diverticula, Am. J. Surg. **75**:570, 1948.

Prolapse of Gastric Mucosa.—Four instances of prolapsed, hypertrophied or redundant gastric mucosa are described.[186] Bralow and Spellberg [187] suggest that benign peptic ulceration may be followed with gastritis, hypertrophy of the gastric rugae and, later, with a prolapse of gastric mucosa into the duodenal bulb. Sixteen cases are reported by Manning and Highsmith.[188] Although no distinctive syndrome was observed, symptoms referable to the gastrointestinal tract were present in all but 1 case. The characteristic roentgenologic finding consists of a circular, or irregularly circular, mushroom-shaped, or umbrella-shaped filling defect at the base of the duodenal bulb, often associated with narrowing and elongation of the pyloric channel, and with antral spasm and enlarged antral rugae. Transpyloric herniation is considered capable of producing vague gastric symptoms, and even hematemesis and melena.[189] Ferguson,[190] on the basis of a study of 6 patients, concludes that whereas patients with "milder" cases respond to special diets and the use of antispasmodic drugs, the curative treatment is surgical; the operation may consist of resecting the prolapsed mucosa, short circuiting the area or enlarging the gastric outlet.

The reviewers have not found it necessary, thus far, to recommend surgical intervention or, indeed, medical therapy, for prolapsing gastric mucosa; the symptoms encountered in patients with this condition usually are attributable to factors other than the prolapse.

Hypertrophic Pyloric Stenosis.—The subject is reviewed by Barker and his associates.[191] Two cases are reported in adults.[192] A girl of 6 weeks with the signs of pyloric stenosis failed to respond to medical treatment and at abdominal exploration was reported not to have pyloric stenosis.[193] Glyceryl trinitrate relieved the symptoms completely. Congenital pyloric stenosis is reported in each of 4 brothers [194]; Ramstedt's

186. Bralow, S. P., and Melamed, M.: Prolapse of Redundant or Hypertrophied Gastric Mucosa, Am. J. Digest. Dis. **14**:215, 1947.

187. Bralow, S. P., and Spellberg, M. A.: Etiology of Prolapsed Gastric Mucosa with an Illustrative Case Report, Am. J. Digest. Dis. **14**:332, 1947.

188. Manning, I. H., and Highsmith, G. P.: Prolapse of the Gastric Mucosa Through the Pyloric Canal Into the Duodenum: Report of Sixteen Cases Diagnosed Roentgenologically, Gastroenterology **10**:643, 1948.

189. Nygaard, K. K., and Lewitan, A.: Transpyloric Herniation of Redundant Gastric Mucosa, Am. J. Surg. **75**:502, 1948.

190. Ferguson, I. A.: Prolapse of the Gastric Mucosa, Ann. Surg. **127**:879, 1948.

191. Barker, H. O.; Hardy, H. H., Jr., and White, H. A.: Hypertrophic Pyloric Stenosis, New Orleans M. & S. J. **100**:307, 1948.

192. Hobson, A.: Hypertrophic Pyloric Stenosis in the Adult, Brit. M. J. **1**:99, 1948.

193. Falle, E. de C.: Pyloric Spasm Simulating Congenital Hypertrophic Pyloric Stenosis: Report of Case, Lancet **1**:794, 1948.

194. Gailey, A. A. H.: Congenital Hypertrophic Pyloric Stenosis: Report of Four Cases in Brothers, Brit. M. J. **1**:100, 1948.

operation was sucessfully performed in each case. The hospital records in 248 cases of pyloric stenosis are reviewed by Schaefer and Erbes.[195] In 9 instances more than 1 member of a family was affected; in 7 instances 1 of a set of twins had the disease. The last 172 patients were operated on without a fatality. Forty-nine patients with congenital hypertrophic pyloric stenosis were treated by the Fredet-Ramstedt operation.[196] No deaths occurred within one month of the operation. One baby died three months later, due to repeated vomiting with aspiration of the vomitus; a duodenal ulcer was found at autopsy. A follow-up study was made of 20 persons on whom the Ramstedt operation for hypertrophic pyloric stenosis had been performed during infancy.[197] The series included one pair of female twins and 2 brothers. The incidence of ulcer and/or nervous disturbances was high in these patients and in their close relatives.

Pyloric Stenosis After Ingestion of Lye.—Pyloric stenosis developed twenty-two days after the ingestion of a solution of lye, taken with suicidal intent; esophageal stricture did not ocur. The symptoms were relieved by a gastroenterostomy.[198]

Jejunogastric Intussusception.—Jejunogastric intussusception was diagnosed roentgenologically in the case of a patient who had previously undergone a partial gastric resection.[199] Moroney[200] reports a similar event occurring six years after a posterior gastroenterostomy.

Volvulus.—Three cases of volvulus of the stomach are described by Robnett and Jones,[201] 5 by Cesarini[202] and 2 by Cardon and his associates.[203]

Acute Dilatation.—Dahl[204] discusses the various causes of "gastrectasia" and presents 20 reports of cases, collected during a four year

195. Schaefer, A. A., and Erbes, J.: Hypertrophic Pyloric Stenosis, Surg., Gynec. & Obst. **86**:45, 1948.

196. Duckett, J. W.: Surgical Treatment of Congenital Hypertrophic Pyloric Stenosis, Texas State J. Med. **43**:320, 1947.

197. Bendix, R. M., and Necheles, H.: Hypertrophic Pyloric Stenosis, J. A. M. A. **135**:331 (Oct. 11) 1947.

198. Belchor-Costa, G., and Resano, J. H.: Estenosis del piloro por caustico sin lesión del esófago, Arch. argent. de enferm. d. ap. digest. y de la nutrición **22**:164, 1947.

199. Aleman, S.: Jejuno-Gastric Intussusception, Acta radiol. **29**:383, 1948.

200. Moroney, J.: Some Interesting Gastrojejunal Lesions, Brit. J. Surg. **35**:374, 1948.

201. Robnett, A. H., and Jones, T. E.: Volvulus of the Stomach, Cleveland Clin. Quart. **14**:239, 1947.

202. Cesarini, M.: Il quadro radiologico del volvolo gastrico sull'asse trasversale nelle sue varietàs cronica e intermittente, Arch. ital. mal. app. diger. **13**:249, 1947.

203. Cardon, L.; Greenebaum, R. S., and Avende, J.: Volvulus of the Stomach, Ann. Int. Med. **27**:455, 1947.

204. Dahl, J. F.: Roentgen Examination of Acute Dilatation of the Stomach, Acta radiol. **29**:237, 1948.

period. These are classified etiologically as (*a*) anatomic dislocations or anomalies, such as volvulus or hiatus hernia, (*b*) organic stenosis of the pylorus or the duodenum by ulcer or carcinoma, (*c*) pressure from extra-alimentary masses or bands, and (*d*) primary gastric dilatation, attributable to circulatory changes or occurring after operation. Several roentgenologic technics are described to differentiate gastric dilatation from other conditions presenting similar clinical features. Four cases of acute dilatation of the stomach in emaciated prisoners of war are described [205]; the cause in each instance was considered to be overdistention of the stomach with food.

Gastric Fistula.—A fistula between the stomach and the left side of the pleural cavity or chest wall may develop spontaneously as a result of perforation of a gastric ulcer or cancer, or as a complication of wounds involving the diaphragm and stomach.[206] Rarely, a thoracogastric fistula may develop when drainage from supposed empyema or effusion proves to indicate incarceration of the stomach in a diaphragmatic hernia. Two cases of the latter type are presented and reparative methods outlined. An instance of post-traumatic gastrobronchial fistula is recorded.[207]

Gastroscopy.—Recent developments in the field of gastroscopy are summarized by Benedict.[208] The value and limitations of the procedure are described by a number of authors.[209] Rodgers [209h] points out that gastroscopy has to its credit many successes, both in the avoidance of abdominal section and in the diagnosis of early gastric cancer. Maur [209i] states the belief that gastroscopy is superior to roentgenologic examination in the demonstration of postoperative lesions in the stomach.

A combination of thiopental sodium U. S. P. (pentothal sodium®) and curare, administered intravenously, is regarded as a highly satisfactory anesthetic.[210]

205. Markowski, B.: Acute Dilatation of the Stomach, Brit. M. J. **2**:128, 1947.

206. Lindskog, G. E., and Lawrence, E. A.: The Treatment of Thoracogastric Fistula, J. Thoracic Surg. **16**:477, 1947.

207. Liavaag, K.: Gastro-bronchial Fistula, Acta chir. Scandinav. **96**:425, 1948.

208. Benedict, E. B.: Endoscopy, New England J. Med. **237**:126, 1947.

209. (*a*) Gibb, W. T., Jr.: The Clinical Aspects of Gastroscopy, Am. Pract. **2**:111, 1947. (*b*) Hampton, H. P.: Clinical Value of Gastroscopy, J. Florida M. A. **34**:312, 1947. (*c*) Friedrich, L.: The Place of Gastroscopy in Diagnosis of Gastric Lesions, Gastroenterologia **72**:216, 1947. (*d*) Stollreiter, H.: Die Bedeutung der Gastroskopie für die Klinik, Deutsche med. Wchnschr. **72**:537, 1947. (*e*) Heineken, T. S.: Conservative Use of Gastroscope, J. M. Soc. New Jersey **45**:61, 1948. (*f*) Mitchell, E. D., Jr.: Gastroscopy in Relation to Gastric Surgery, South. Surgeon **13**:521, 1947. (*g*) Barowsky, H.: Indications and Contraindication for Gastroscopy, Am. J. Digest. Dis. **15**:10, 1948. (*h*) Rodgers, H. W.: Gastroscopy in the Diagnosis of Gastric Cancer, Brit. J. Radiol. **20**:502, 1947. (*i*) Maur, M.: La endoscopía del estómago operado: Su valor comparado con la radiologia in 157 casos, Arch. argent. de enferm. d. ap. digest. de la nutrición **22**:311, 1947.

210. Stempien, S. J., and Greene, W. W.: Gastroscopy Under Pentothal-Curare Anesthesia, Gastroenterology **10**:978, 1948.

Colcher [211] attached a transparent balloon to the lower end of the gastroscope for distention of the stomach. The balloon, when inflated, straightened the lesser curvature and made possible a more complete gastroscopic examination. The formerly blind areas of the lesser curvature of the antrum and the posterior portion of the wall of the corpus were visualized in 12 of 13 cases. Gill and Highton [212] describe a method of binding a tube to a gastroscope so that fluid may be removed from the stomach during gastroscopy.

Segal and Watson [213] describe their ingenious apparatus for taking colored photographs through the flexible gastroscope. The apparatus consists of (*a*) a flexible gastroscope, the glass elements of which have been coated to improve the transmission of light; (*b*) a lamp of increased wattage; (*c*) a camera with a coupling device, a periscope and a floating support, and (*d*) a power supply and synchronization unit. Satisfactory color transparencies were obtained with 35 mm. type A Kodachrome® film; exposure time was one-half second.

Two additional instances of pneumoperitoneum after the passage of the flexible gastroscope are reported [214]; both patients recovered. The authors conclude that penetration of the gastric wall by air is rarely serious, and that surgical intervention usually is not required. Witherspoon [215] reports a perforation of the esophagus after gastroscopy; mediastinotomy (superior anterior section) was performed, with complete recovery.

Appearance of Mucosa After Vagotomy.—Wolff [216] performed gastroscopy in 8 cases of duodenal ulcer and 3 of gastric ulcer, one week to eleven months after vagotomy. The mucosa appeared dull and reddened in 7 and normal in 4. Gastric tonus was diminshed; there were retention of food, blunting of the angulus and obliteration of the musculosphincter antrums. The last two symptoms disappeared temporarily in the 3 cases in which carbaminoyl-beta-methylcholine chloride (urecholine®) was given subcutaneously.

211. Colcher, H.: Gastroscopy with Transparent Balloon: Method for the Visualization of the Blind Areas, Am. J. Med. **3**:423, 1947.

212. Gill, A. M., and Highton, T. C.: Combined Gastroscope and Suction Tube, Lancet **2**:655, 1947.

213. Segal, H. L., and Watson, J. S.: Color Photography Through the Flexible Gastroscope, Gastroenterology **10**:575, 1948.

214. Chamberlin, D. T.: Pneumoperitoneum Following Gastroscopy Apparently Without Perforation, New England J. Med. **237**:843, 1947. Wilson, J. A., and Reid, H. W.: Pneumoperitoneum with Spontaneous Recovery Following Use of the Flexible Gastroscope, Gastroenterology **10**:731, 1948.

215. Witherspoon, W. M.: Case of Hour Glass Stomach, Gastroscopy, Perforation of the Esophagus and Recovery, Gastroenterology **10**:540, 1948.

216. Wolff, R.: The Gastroscopic Appearance of Gastric Mucosa Before and After Vagotomy, Gastroenterology **10**:231, 1948.

Incidence of Gastritis.—McGlone,[217] in a report of gastroscopic observations made in the South Pacific over a period of twenty months, states that gastroscopy was of value not only in making the diagnosis of gastritis but also in eliminating many clinical diagnoses of gastritis. Gastritis was diagnosed in only 25 cases in which patients were admitted to a hospital; the patients did not present a uniform or characteristic clinical picture. The observations coincide, in general, with the experience of the reviewers.

Diagnosis of Gastritis.—Feldman[218] states that mucosal abnormalities and filling defects of the greater curvature of the stomach must be interpreted cautiously. Repeated roentgenologic and gastroscopic studies, together with thorough clinical investigation, frequently are necessary for proper evaluation.

Gastritis with Hemorrhage.—Two cases of gastritis with hemorrhage are described.[219]

Hypertrophic Gastritis.—In the case of a patient with a disorder diagnosed at gastroscopic examination as chronic hypertrophic gastritis and with characteristic, cobblestone-like mucosa, a biopsy specimen from the stomach disclosed a most unusual perivascular infiltration and vascular necrosis. The surface epithelial cells and the pyloric glands were well preserved and normal.[220] A case of giant hypertrophic gastritis with the characteristic appearance of cerebral convolutions is described.[221] In a series of 30 patients with chronic hypertrophic gastritis, none, as might have been expected, showed improvement at clinical or gastroscopic examination after short wave diathermy[222]; the rationale is open to question.

Postoperative Gastritis.—Palmer,[223] in an analysis of the cases of 24 patients undergoing gastric surgery, concludes that the chronic gastritis engendered by surgical intervention is of the superficial atrophic type. The secretory activity of the stomach after operation does not play a significant role in the development of gastritis, nor does rhythmic

217. McGlone, F. B.: Observations on Gastritis Based Upon Experience in a General Hospital in the South Pacific, Gastroenterology **10**:681, 1948.

218. Feldman, M.: Mucosal Deformities of the Greater Curvature of the Stomach, Radiology **49**:152, 1947.

219. Chipman, I. L.: Hemorrhage Associated with Gastritis, U. S. Nav. M. Bull. **48**:253, 1948.

220. Schneider, H., and Dailey, M. E.: An Unusual Type of Gastritis, Gastroenterology **10**:727, 1948.

221. Bourne, W. A., and Wood, W. A. F.: Giant Hypertrophic Gastritis, Proc. Roy. Soc. Med. **41**:42, 1948.

222. Palmer, E. D.: Observations on the Treatment of Chronic Hypertrophic Gastritis with Shortwave Diathermy, Rev. Gastroenterol. **15**:233, 1948.

223. Palmer, E. D.: Observations on the Etiology of Postoperative Gastritis, Gastroenterology **10**:671, 1948.

activity of the stoma protect against its occurrence. Chronic gastritis after operation is regarded as an important complication of gastric surgery.

Mucosa in Pernicious Anemia.—Hardt and his associates,[224] in a gastroscopic study of 100 patients with pernicious anemia, found atrophy of the stomach in only 59 per cent. The atrophy was not related to the duration of the disease, the amount of previous liver therapy or the condition of the blood at the time of the examination. Only 9 of the 47 patients with atrophy manifested improvement in the appearance of the mucosa during liver therapy. Polyps were found in 7 cases and a proved carcinoma in 1, the latter developing while the patient was receiving liver.

Phlegmonous Gastritis.—A case of phlegmonous gastritis secondary to resection for gastric ulcer is reported.[225] The lesion was diagnosed roentgenologically on the basis of obliteration of mucosal folds and apparently increased thickness of the gastric wall. In the case of a boy of 18,[226] severe epigastric pain and fever developed approximately two weeks after admission to a hospital for measles; the leukocyte count rose to 24,000 per cubic millimeter. Operation revealed pronounced induration of the distal two thirds of the stomach, with a fluctuant mass in the antrum; culture of the material aspirated from the abscess yielded hemolytic streptococcus. Recovery followed gastrostomy, drainage of the abscess and the administration of penicillin and sulfadiazine. Bendixen [227] reports a cure with penicillin.

Emphysematous Gastritis.—Emphysematous gastritis apparently developed in 1 reported case after acute gastroenteritis.[228] Escherichia coli, nonhemolytic streptococcus and Staphylococcus aureus were cultured from the gastric content. The recovery of the patient may have been due to the large quantities of penicillin administered.

Gastritis in Allergy and Amebiasis.—Afendulis [229] speculates on the relation of amebiasis and allergy to gastritis. In the opinion of the

224. Hardt, L. L.; Schwartz, O., and Steigmann, F.: Gastroscopic Observations in Pernicious Anemia, Gastroenterology **10**:108, 1948.

225. Lindblom, K.: Roentgen Diagnosis of Phlegmonous Gastritis, Acta radiol. **28**:33, 1947.

226. Guzzetta, P. C., Jr., and Southwick, H. W.: Acute Phlegmonous Gastritis, Surgery **22**:435, 1947.

227. Bendixen, K.: Phlegmonous Gastritis Cured by Penicillin, Nord. med. **33**:780, 1947.

228. Welch, C. E., and Jones, C. M.: Emphysematous Gastritis, New England J. Med. **237**:983, 1947.

229. Afendulis, T. C.: Gastritis and Amebiasis: A Gastroscopic Study, Am. J. Digest. Dis. **15**:13, 1948; Observations in Acute Allergic Gastritis, ibid. **15**:90, 1948.

reviewers, the gastric changes described by the author as taking place in 25 patients with amebiasis do not differ from those usually encountered in persons without amebiasis or allergy.

Congenital Cystic Hyperplasia.—An elderly Negro with anorexia, loss of weight, epigastric pain, gastric anacidity and multiple gastric filling defects underwent a partial gastric resection. The stomach was involved by diffuse cystic hyperplasia of the mucosa and submucosa, and an abscess was present in a cystic structure in the prepyloric area. The authors state the belief that the process was related to a developmental defect in the gastric glands.[230]

Gastric Syphilis.—Schwartz,[231] in a study of 12 cases of secondary gastric syphilis, found that the gastroscopic picture was similar to that in chronic superficial gastritis, with reddening, increased highlights, edema and adherent mucous patches. The symptoms disappeared in 10 cases after treatment with penicillin; acid values subsequently became normal in 7 cases, hypochlorhydria remained in 4 and achlorhydria slowly changed to hypochlorhydria in 1.

Patterson and Rouse [232] studied the gastroscopic features in 14 cases of tertiary gastric syphilis, selected from a total of 16,714 cases of seropositive syphilis. The findings were described as ulcerating and ulceronodular lesions in 8 cases; nodular or gummatous tumors without ulceration in 3, and infiltrative or leather bottle stomach in 3. The livid or slightly brownish to violaceous color of the mucosal margins of the ulcers was determined histologically to be due to a fibrosing, obliterating panvasculitis of the submucosa. The ulcers, in the absence of hydrochloric acid in the gastric secretion, were not peptic ulcers, but rather, necrotic defects due to curtailment of the normal blood supply to the region. At gastroscopic examination, the livid hue of the mucosal margins about the syphilitic ulcers thus appear somewhat different from the normal pink color of the mucosa about a peptic ulcer or the fiery red color of the highly vascular margins of the ulcerating carcinoma. The description of the different types of syphilitic lesions before and after treatment is of particular interest.

Knight and Falk [233] report an unusual case in which tertiary syphilis produced a constricting hourglass deformity of the stomach. At opera-

230. Scott, H. W., Jr., and Payne, T. P. B.: Diffuse Congenital Cystic Hyperplasia of Stomach Clinically Simulating Carcinoma, Bull. Johns Hopkins Hosp. **81**:448, 1947.

231. Schwartz, I. R.: Gastroscopic Observations in Secondary Syphilis, Gastroenterology **10**:227, 1948.

232. Patterson, C. O., and Rouse, M. O.: Description of Gastroscopic Appearance of Luetic Gastric Lesions in Late Acquired Syphilis, Gastroenterology **10**:474, 1948.

233. Knight, W. A., and Falk, A.: Tertiary Gastric Syphilis, Gastroenterology **9**:17, 1947.

tion, an ulcerating, infiltrating lesion, with the characteristic histologic appearance of a syphilitic lesion, was found on the greater curvature. In another case of syphilis, gastroscopic examination revealed five sessile, polypoid elevations, 0.5 to 1 cm. in diameter, in the antrum and body, with a shallow ulcer near one of the polypoid lesions. Antisyphilitic therapy was given, and a normal gastric mucosa was observed six months later.[234]

The clinical symptoms in a case of gastric syphilis resembled those of ulcer, and the roentgenologic appearance simulated cancer.[235] The correct diagnosis was established by histologic examination of the resected specimen. In another case,[236] a lesion of gastric syphilis simulated a cancer of the antrum; the lesion disappeared after appropriate therapy. Weber [237] reports still another case of syphilitic ulcer. Antisyphilitic therapy alone [238] is reported to have produced striking therapeutic effects in patients with both gastric ulcer and syphilis.

Tuberculosis.—A case of gastric tuberculosis in a Negro of 23 is reported.[239] The patient died of peritonitis after a partial gastric resection. Histologic examination revealed typical tuberculosis of the stomach, the duodenum and the omental lymph nodes, with acid-fast bacilli. Results of inoculations of animals were negative. No primary focus was found at autopsy. In the case of a man of 52,[240] a tuberculous gastric ulcer was found 6 to 7 cm. below the cardia, on the lesser curvature. Roentgenologic examination demonstrated an old tuberculous focus in the lungs.

Antianemic Factor.—The feeding of 100 Gm. of dried, powdered and defatted stomach wall from the fundal part of the human stomach to a patient with pernicious anemia over a period of eight days produced a striking therapeutic effect; 80 Gm. prepared from the pyloric part of the stomach produced only a moderate therapeutic effect.[241]

234. Rafsky, H. A.; Weingarten, M., and Herzig, W. F.: Syphilis of the Stomach, Rev. Gastroenterol. **15**:359, 1948.

235. Montenegro, C.; Correia, P., and Yoshimoto, M.: Sifilis gástrica, An. paulist. de med. e cir. **53**:124, 1947.

236. Chêne, P.; Pillet-Savaton, and Simon, A.: La syphilis gastrique à forme pseudonéoplasique, Presse méd. **55**:874, 1947.

237. Weber, G.: Syphilitic Gastric Ulcer, Deutsche med. Wchnschr. **73**:163, 1948.

238. Backlund, B., and Cedercreutz, C.: Gastric Ulcer-Gastric Syphilis, Nord. med. **35**:1631, 1947.

239. Morris, H. R.: Gastric Tuberculosis, Am. J. Roentgenol. **59**:682, 148.

240. Raffaele, N.: Contributions to the Knowledge of the Surgcial Forms of Gastric Tuberculosis, Gior. ital. chir. **3**:446, 1947.

241. Landboe-Christensen, E., and Plum, C. M.: Experimental Study on the Localization of Castle's Intrinsic Factor in the Human Stomach, Am. J. M. Sc. **215**:17, 1948.

(To Be Continued)

News and Comment

GENERAL NEWS

International Congress on Rheumatic Diseases.—The Seventh International Congress on Rheumatic Diseases will be held at the Waldorf-Astoria Hotel, New York, from May 30 to June 3, 1949. The congress is sponsored and supported by several organizations, including the American Rheumatism Association, the United States Public Health Service and the Arthritis and Rheumatism Foundation.

Dr. W. S. C. Copeman, who will speak on fibrositis, is the delegate from Great Britain; Dr. Fernando H. Ramos, the official delegate from Uruguay, will speak on "The Painful Shoulder"; Dr. A. R. Moreno, of Buenos Aires, represents Argentina officially and will present a paper on "Possible Relations between Rheumatic Disease and Allergy: Its Experimental Study in the Rabbit." Many other distinguished visitors will take part in the sessions, and many of them will go on to Atlantic City, N. J., for the Annual Session of the American Medical Association, at which there will be several scientific exhibits on rheumatic diseases, and papers on the subject will be read in various sections.

A postconvention tour is planned for the sixteen days following the session of the American Medical Association. Philadelphia, Boston, Buffalo, Detroit, Chicago, Rochester, Minn., and Washington, D. C., will be the cities visited. Scientific sessions will be held at Philadelphia, Boston and Rochester. Sight-seeing motor coaches will be provided in Boston, Washington, Niagara Falls and Chicago. Inquiries concerning registration, the complete program and other aspects of the congress should be addressed to Mr. Robert D. Potter, Executive Director, 535 Fifth Avenue, New York.

Association of Railway Surgeons.—The Sixty-First Annual Meeting of the American Association of Railway Surgeons will be held at the Drake Hotel, Chicago, on Thursday, June 30, Friday, July 1, and Saturday, July 2, 1949.

A scientific session will be held from 10 to 12:30 a. m. and 2 to 4:30 p. m. on each day. Afternoon sessions will be devoted to symposiums on "Lesions of the Bones and Joints" and "Intra-Thoracic Disorders."

Book Reviews

Textbook of Bacteriology: The Application of Bacteriology and Immunology to the Diagnosis, Specific Therapy and Prevention of Infectious Diseases for Students and Practitioners of Medicine and Public Health. Revised by David T. Smith, M.D., and others. Ninth edition. Price, $10. Pp. 992, with 251 illustrations. New York: D. Appleton-Century Company, 1948.

Needless to say, this is still a good textbook of bacteriology. The ninth edition was revised by a group of bacteriologists from Duke University School of Medicine led by Smith and Martin. This edition remains much the same as the previous one except for additions made necessary by recent developments, including those evolved as a result of World War II. Among the additions are excellent electron micrographs and discussions of the antibiotics. The sections on bacterial metabolism and fungus and viral disease were rewritten to bring the discussion up to date. This edition is to be recommended to students and physicians as a single volume textbook of bacteriology.

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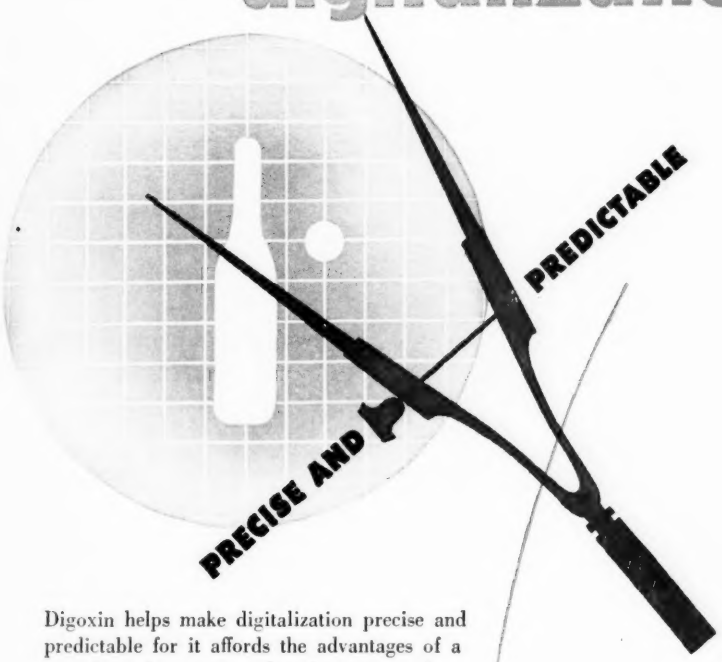

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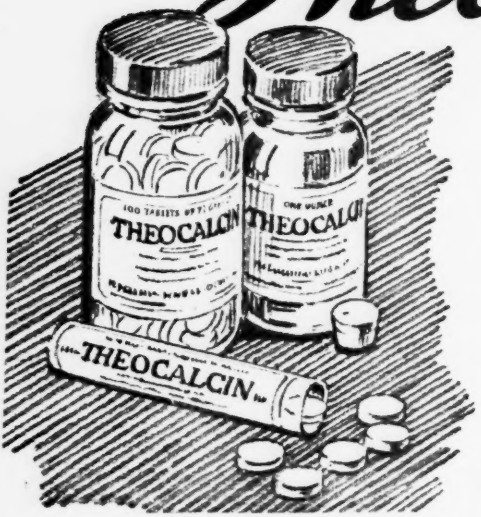

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*Beams, A. J., and Endicott, E. T., Histologic changes in the livers of patients with cirrhosis treated with methionine, Gastroenterology 9:718-735 (Dec.) 1947

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